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

TRANSCRIPT

From Schizophrenia to Alzheimer's: Understanding the KarXT Clinical Trials

Date: October 15, 2026
Featuring: Paul Newhouse, MD

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

NANCY KEACH: From BrightFocus Foundation's Alzheimer's Disease Research program, I'm Nancy Keach. Welcome to the 49th episode of Zoom In on Dementia and Alzheimer's. This program is generously sponsored by Lilly, Biogen, Eisai, and Genentech. And we are deeply grateful to these sponsors for making these free programs possible.

So, welcome, everybody. And today's program is "From Schizophrenia to Alzheimer's: Understanding the KarXT Clinical Trials." And I'm delighted to introduce today's guest expert. Dr. Paul Newhouse holds the Jim Turner Chair of Cognitive Disorders at Vanderbilt University School of Medicine. He is professor of psychiatry, pharmacology, and medicine, director of the Center for Cognitive Medicine, and clinical core director of Vanderbilt's Alzheimer's Disease Research Center. Welcome, Dr. Newhouse.

DR. PAUL NEWHOUSE: Thanks for having me, Nancy.

NANCY KEACH: Great to have you.

DR. PAUL NEWHOUSE: Glad to be here.

NANCY KEACH: So I've been in this field for about 17 years, funding research for Alzheimer's and related dementias. And until this week, when I started preparing for this episode, I really didn't know anything about KarXT. So we're going to try to cover a lot of ground today. I want to cover what KarXT is and how it works, just high level, its potential uses in Alzheimer's disease for agitation, psychosis, and possibly for improving cognitive function.

I want to talk about the clinical trials that are currently recruiting that are testing KArXT, and how our audience can find information about how to participate in those trials.

And then I'm hoping we can talk a little bit about the LiBBY trial and other trials that you've been involved in for things that might help people in moderate and later stages of Alzheimer's. Let's start at the beginning. What is KarXT? And why are Alzheimer's researchers interested?

DR. PAUL NEWHOUSE: Thanks, Nancy. So KarXT is actually a combination drug. It is a drug that has a active ingredient called xanomeline– starts with an X, actually. And it has another drug in it, which is used to block the peripheral side effects of xanomeline. And so it's a one-two combination drug. So xanomeline has been around a long time. We've known about it. It was developed, actually, by Lilly about 25 years ago. And we were very excited about it at the time.

But its trials, when it was used by itself, had just too many side effects. And so some clever folks at Lilly, and, actually, outside of Lilly with the original company that came out of Lilly, said, well, why don't we actually combine it with a drug that will block some of those side effects? And that's a very clever idea. And so they took a drug that's been on the market for a long time, which is used for bladder problems and things like that, and they combined it with xanomeline to produce KarXT, also now called Cobenfy.

And so this combination drug was first tried in schizophrenia, which is a psychotic disorder, a disorder of delusions and hallucinations. And it was shown to have significant benefit in patients with this disorder. Now, that was quite remarkable because it was the first drug of this chemical class that really had significant benefits on behavior and delusions and hallucinations and emotional problems in schizophrenia.

And so the natural question that many of us wanted to ask was, well, if it works on psychotic symptoms and delusions and hallucinations over here in schizophrenia, could it also have benefit in patients with Alzheimer's disease? And so that has led to the current program that Bristol Myers Squibb has launched now to examine the potential for treatment benefit in patients with Alzheimer's disease.

NANCY KEACH: And is this a pill? Is this an oral drug?

DR. PAUL NEWHOUSE: This is an oral medication. That's correct.

NANCY KEACH: And so, in very simple language, can you explain how it works in the brain?

DR. PAUL NEWHOUSE: Sure. So xanomeline, or Cobenfy– KarXT, the same thing– is what we call a direct agonist. Now, let me explain what that means. That means that it directly stimulates nerve cells at something called the cholinergic receptor. And the cholinergic receptor is an ancient receptor in the brain, phylogenetically very old, goes

all the way back to primitive animals. And we have that system in abundance in our human brain. And that system is critically important for controlling attention, memory, emotional processing, emotional control, and a whole host of other systems in the brain.

And so it was identified many, many, many years ago that the cholinergic system is greatly impacted by Alzheimer's disease. In fact, it was one of the first chemical systems that was identified as being damaged. And so a lot of us– myself included– as far back as the 1980s began to experiment with drugs to try to stimulate that system. But the tools we had were very, very difficult. And xanomeline now is a more advanced way of stimulating that system, essentially squeezing more juice out of the lemon. And so, yes, the system is damaged, but maybe we can make it work more efficiently and more effectively. And that's what KarXT hopes to do.

NANCY KEACH: And so how is the mechanism of action, the way it works, and its effects different from medicines like Aricept, or donepezil, or from the anti-amyloid treatments that have been approved, like Leqembi and Kisunla?

DR. PAUL NEWHOUSE: That's a great question. So the older drugs like Aricept or donepezil or rivastigmine, galantamine, those are drugs that have been around now for over 30 years. And those drugs were a triumph at the time. They were the first orally available, what we call cholinesterase inhibitors. And what that means is, they don't directly stimulate themselves. What they do is they stop the breakdown of the native chemical in the brain called acetylcholine. Well, that's good, but it's an indirect way of solving the problem, right?

NANCY KEACH: Right.

DR. PAUL NEWHOUSE: And so those had some benefit, and they still are used. They have some benefit, but they don't provide substantial benefit because they have too many side effects. If you push the dose, people get sick. They don't feel well. They had nausea, et cetera. And we've never had a drug that directly bypasses that system and stimulates their nerve cells directly. And so that's what xanomeline or KarXT will do.

Now, that has limitations of its own. That's a more technical discussion, but it's definitely a step forward. The drugs like Leqembi and the antibodies that have been approved more recently, that's a very different mechanism of action. And that really gets to a different problem. So drugs like Leqembi focus on the underlying protein abnormalities in Alzheimer's disease. And drugs like donepezil or KarXT will focus on the downstream damage that's caused by those proteins.

And so you can see that they really could be very complementary to each other. And actually, you could imagine that hitting both targets will actually benefit the patient than either one or the other by itself. That's what we hope.

NANCY KEACH: And that's exactly what I was thinking, is, could we see a world where these are combined, and they might be combined with a 40 Hertz– a light and sound thing and different combinations, cocktail of treatments?

DR. PAUL NEWHOUSE: That's right. That's right. Cancer treatment, we know, is often multi-drug. I mean, we use multiple different treatments to attack cancer from this angle and that angle and this angle. And we have to do that with Alzheimer's disease. And combination, or what Reisa Sperling has called COMBAT– Combined Alzheimer Therapy– COMBAT, right? So she's coined the term COMBAT. And I think that is an appropriate idea that we do have to really combine treatments.

NANCY KEACH: And what do we know now about the safety profile for KarXT of today, especially for older adults potentially taking other medications? I have a question that was sent in by Lois in Miami, Florida, "Also, is ARIA a side effect of this drug?" So if you can talk about side effects.

DR. PAUL NEWHOUSE: So the side effects of KarXT are actually quite well-known because we've known about this system for 40, 50 years. So when you overstimulate cholinergic receptors in the body, you get salivation. You get nausea. You might get diarrhea. You might get sleep disturbance. Those are all very well-known side effects from drugs like Aricept.

Well, KarXT has a very similar profile. What we hope is that combining this with this peripheral drug, which blocks those side effects, will dramatically improve the situation. And so we know very well what the side effect profile is. And it's very different from drugs like Leqembi. There's no ARIA. It doesn't interact with amyloid protein directly. It doesn't interact with tau protein directly. So it works in, if you can imagine, overlapping circles. It has its own mechanism, but there's hopefully some combination benefit of the two approaches.

We think that the side effect profile is very manageable. The question always is, with cholinergic drugs, is, can you get the benefit and still avoid side effects that people will say, I just don't want to take this drug anymore? Because no one wants to feel nauseous. No one wants to be running to the bathroom. No one wants to be sweating or salivating too much. So those are well-known problems. And I think KarXT safety profile looks really quite good.

NANCY KEACH: John wrote into the chat, "Leqembi is not yet fully covered in Canada. How long would it take for this drug to be covered here?" So I was going to ask this much later in the program, but we might as well jump in and talk about the time frame here, because these drugs now are just in these phase III trials. So let's imagine that the three trials we're going to talk about today, which are MINDSET, ADAGIO, and ADEPT, let's say any of them are positive. I know you have no crystal ball, but what's a general timeline that we might expect, if there is positive results– that's an if– that we might see an approval and then, later, potentially, coverage?

DR. PAUL NEWHOUSE: Well, first of all, I think it should be understood that Cobenfy, or KarXT, is actually already FDA-approved. So it's FDA-approved for schizophrenia. It could be prescribed off-label today. And so, it doesn't have to go through its very long FDA approval cycle. So what BMS is trying to do here is, they're trying to get additional indications for this agent, which is a common thing that drug companies do. They want to expand the market. And so I would imagine that if these studies read out positively, let's say, in 2027, and all of them read out positively, or one or more of them read out positively, I think it would be mid to late 2028 before we would see FDA approval of these extra indications.

NANCY KEACH: And is Cobenfy approved in Canada? Do we know?

DR. PAUL NEWHOUSE: I actually don't know that.

NANCY KEACH: OK. But it sounds like, again, if there's positive results, it could be used off-label.

DR. PAUL NEWHOUSE: That's correct.

NANCY KEACH: But then, would it potentially be covered? And I think we're talking again about US right now.

DR. PAUL NEWHOUSE: I mean, boy, you'd need an expert on insurance coverage. My guess is that it won't be covered initially, not without a diagnosis of schizophrenia. So I think it might be a little bit difficult to obtain coverage, until there's an FDA indication. My guess is that Medicare won't cover it, for example.

NANCY KEACH: Immediately.

DR. PAUL NEWHOUSE: Immediately, yeah.

NANCY KEACH: Right. So we'll keep you posted when this drug reads out on the timelines, as they happen in real-time, for potential coverage. So I want to talk a little bit about– we've talked about agitation and psychosis. Can you just go back to basics

here and explain how are agitation and psychosis are different? And can someone be experiencing them both?

DR. PAUL NEWHOUSE: So agitation we operationally define as distress without some obvious cause. So that would be someone who could be anxious, for example, but they can't control the level or the emotional expression of their anxiety. Or they might be distressed because they're in pain, for example, or agitated because of that. They might be angry.

And one of the problems in Alzheimer's disease is that the brain disease robs people of the ability to control their emotional expression. And so you and I and all the people on this call have learned to modulate our emotional response to things. We might become irritated, or we might become anxious, but we can usually control that and control the expression. But what Alzheimer's disease does is it damages those systems in the brain that modulate emotional expression. That can produce agitation, even to very minor stimuli.

Psychosis is a little bit different, or as my Polish colleague like to say, it's the same, but a little bit different. And so psychosis represents a disconnection from reality. It means that you are seeing or hearing or believing things that are not occurring or not there. So a psychotic symptom might be a delusional belief, for example, that your wife is having an affair, or someone has been stealing from your room in the nursing home.

And other symptoms of psychosis can include hallucinations. For example, I see animals, or I see things that aren't there, or I see people that aren't there. When my late mother, who had Parkinson's disease, had hallucinations, and she was smart enough to recognize that, and she would say, I saw you the other day at the house. I know you weren't there, but there you were.

And what we think is happening in the brain, Nancy, is that essentially, the internal world becomes predominant. When we dream, you and I have, essentially, things happen in our brain, and it seems real. Well, can you imagine that dreams now break through to waking, and now you have trouble distinguishing what's internal versus what's external? And we think the cholinergic system is part of the mechanism that helps us distinguish internal reality from external reality.

And so the cholinergic system helps us do that. And when that system is damaged, those internal realities can break through. And now you can't distinguish what's real and what's not, or what's happening outside of your body and what's happening inside your head. And so hallucinations and delusions can occur without agitation, but the two often go together.

NANCY KEACH: Understood. Pauline is asking, "Is the agitation cause similar in other forms of dementia besides Alzheimer's?" And I know hallucinations or delusions are more predominant in certain other related dementias, if you want to talk about that a little bit.

DR. PAUL NEWHOUSE: Right. Again, to quote my Polish colleague, it's the same, but a little bit different. So yes, hallucinations and delusions occur in Lewy Body Dementia, in Parkinson's disease. And so we certainly see those problems. And there are certain characteristics. For example, we know that people with Lewy Body Dementia tend to see more formed hallucinations, usually people or animals, things like that. That's not as common in Alzheimer's disease, but they can still see visual hallucinations.

I mean, one of the classic symptoms when I was first in practice was that I would see an elderly woman in my clinic who would tell me that she had children living in the house, because she could hear the children or see the children. And we know that that's a hallucination. There were no children living in her house. And so that would be a common symptom in those days, what people would present with.

Now, auditory hallucinations, hearing things is more common in schizophrenia. It's less common in Alzheimer's disease, interestingly. We don't know the reason for that, but that's something that we've observed clinically. Visual hallucinations are more common in dementia of all types, and auditory tends to be more common in schizophrenia.

NANCY KEACH: Before we go to the clinical trials, which I want to do– and Tracy had asked if there was any preliminary data available. So before we get into the trials and the data, someone named Chris, asked a question that I thought was interesting and that you would be able to answer. "My wife has early onset Alzheimer's disease, and she has been on Cobenfy for about a year. Her delusions have decreased, but they have not been eliminated. Do you have any advice on how to further decrease delusions?"

So I don't know if this is something you study, so I don't mean to put you on the spot. But I thought that if this reduces, are there other things that one can do to help reduce delusions? And somebody else had asked in the question– Rebecca, "You mentioned that agitation is distress without cause. So might that include overreactions to seemingly minor issues?" So I just want to ask, because you are an expert in agitation and delusion, some of those questions.

DR. PAUL NEWHOUSE: So just to answer the last question first, yeah. So let me clarify, of course, there can be a reason for agitation. And it can be very minor, like somebody's visiting, or somebody leaves, or they see something that is distressing or hear something that's distressing, or they see a picture. We've even had people become

agitated to seeing a picture of someone, perhaps, or the realization that their loved one is going to leave today or is not visiting the nursing home or the memory care facility.

So agitation can occur in response to normal events, like getting dressed or having a bath or something like that. So normal procedures, if you will. And so agitation can be either spontaneous or in relation to a problem. But it can be, like you said, quite minor. To go back to the first question, then, about what can be done to even further improve someone's symptoms of psychosis or delusions, again, this is one of those– the art of medicine, carefully combining treatments, such as Cobenfy, which might improve the situation, but might not get rid of it entirely. It might be useful to combine that with one of the more atypical antipsychotics at very low dose. That might help someone's psychosis resolve.

Most of my career, I've been treating patients with carefully combining therapies so as I don't get too many side effects from one. And so my advice would be to have a geriatric psychiatrist or someone similar examine the individual's wife and see if there can be other medications that could optimize her therapy. But it's often possible to do that. Sometimes, you run into a problem where you get too many side effects, and you can't get rid of all of the symptoms, but you can usually reduce the distress that it produces for everybody.

NANCY KEACH: I think this is really fascinating, and I'm going to ask one more question about agitation before we move into the trials. There are a couple of drugs, and you mentioned a little bit, approved for agitation. Rexulti and Auvelity are the brand names. So if KarXT is effective in agitation, will it be different than Rexulti or Auvelity or complementary? Will it have the same effects? What's your take?

DR. PAUL NEWHOUSE: Well, it's hard to say because head-to-head trials are rarely ever done by pharmaceutical companies.

NANCY KEACH: Ah.

DR. PAUL NEWHOUSE: But the beauty of having Cobenfy approved, if it does get approved, is that we would now have three drugs with three completely different mechanisms of action, which shows you a couple of things, really. One is that the brain is a very complex organ, and you can get, essentially, a handle on these different symptoms by interacting with one or more different neurotransmitter systems in the brain.

And so I would be very positively inclined if the Cobenfy gets approved for this because I think it would offer us another tool. And one of the great things about pharmacology

is to get multiple tools because we don't want just "Me Too" drugs. We don't want a drug that gets approved that's really pretty much the same as a prior drug. It's just a slightly different molecule.

We like different mechanisms of action because everybody's different. Every patient may respond to one drug, but not to another. And so it allows us more, I used to tell the students, arrows in my quiver. It gives me more arrows in my quiver that I can aim at the patient to see if it will help. So I would be very excited by that.

NANCY KEACH: OK, let's move now to the KarXT clinical trials. And we received, overwhelmingly, the most questions from our audience in advance about how to participate in the trials, how can they find out what the criteria are. I have Jean from Carlisle, Pennsylvania, "What's the best way to find out about a clinical trial?" Gail from Hayward, California, "Where can I sign up to become part of a test group? I have had disease for two years. I'm willing to travel anywhere in the US, and I'm located near UCSF or Stanford." "How can I volunteer?" from Vicki in Benbrook, Texas.

And a lot of people asked eligibility questions. Jim from Georgetown, Texas, "Are there test programs that an 87-year-old woman would qualify for?" Toby asks, "What if a patient is on Leqembi?" So we're going to get into this now. I want to give the audience a place to go to look for trials. So on the screen now shows a link to brightfocus.org/clinicaltrials. That is BrightFocus Foundation's clinical trial finder. And it is a little easier to use than clinicaltrials.gov, which is the central clinical trial finder system in the US. But of course, anyone can access either of these, brightfocus.org/clinicaltrials.

So you can go to this link. You can put in the name of the trials, and you'll see them on the bottom– MINDSET, ADAGIO, and ADEPT. And you can look to see if there is a site near you that is recruiting people to participate in the trials and what is called the eligibility criteria. That is, it would indicate that you may be eligible or what are exclusion criteria, what might mean that you can't go into that trial.

So this is a place to begin. And we mentioned earlier that this is a medication that Bristol Myers Squibb is developing. And so if you want to go right to the source to ask questions of the company, these are the helplines that they've put out. Telephone is 855-907-3286. And the website that they offer is bmsclinicaltrials.com. I hope this is helpful to determine if you or your loved one might be eligible for one of these trials.

So we have MINDSET, ADAGIO, and ADEPT. And there's a couple of iterations of each. And they're each studying KarXT for a different indication. So Dr. Newhouse, which one would you like to start with? Do you have a preference?

DR. PAUL NEWHOUSE: Yeah, I mean, I'm really only knowledgeable, frankly, about ADEPT because our center has been involved with the ADEPT trial. So this is a study of agitation. And it involves patients who have suffered from Alzheimer's disease, who have biologically confirmed Alzheimer's disease, and who have not been adequately managed on their current medical regimen.

Their agitation persists, and they have significant distress. They have to meet certain criteria for how much distress. And it has to have significant impact on their family and their caregivers, et cetera. And so that's the trial, ADEPT. I'm less familiar with the other two because we're not involved with them at our site. But that's the ADEPT trial. But the other ones focus more specifically on psychotic symptoms, like delusions and hallucinations, and just cognitive improvement in the third one.

NANCY KEACH: And I have, for ADEPT, I tried to print out some eligibility criteria, although these sometimes change and vary over the course of time, so you have to check what is currently on the trial listing. But for ADEPT, I have an age of 55 to 90, so there's an answer to the man who asked if an 87-year-old woman might be eligible. For this ADEPT– this is number 1, 2, and 4, so there are different tests going on– 55 to 90 and with a possible or probable diagnosis of Alzheimer's. There are other eligibility criteria, but that's the basis for the ADEPT trials.

And the ADAGIO, I believe, is testing for psychosis. And the eligibility criteria for that says adults with Alzheimer's disease. And then they ask us to confirm the applicable age range with the study site that's near you, if there is a site near you. And you also need the 2024 Alzheimer's Association Diagnostic Criteria. And so I was actually trying to look into you have to have a diagnosis of mild cognitive impairment or early Alzheimer's disease.

And we've done several episodes about getting a diagnosis. And we know that, essentially, there are now blood tests to confirm. There are PET scans. And there is the deathly feared lumbar puncture, which is actually not to be deathly feared. But which one of those or combination of those you might need will depend on the study site, again. So you might just need an Alzheimer's blood test. You might have to go on for a PET scan. And Dr. Newhouse, correct me if I'm wrong, but I don't think there's too many places where you must get a lumbar puncture now. But am I correct?

DR. PAUL NEWHOUSE: That's correct. For most Alzheimer's studies– not all, but most– a lumbar puncture is not necessary to confirm a diagnosis. So we now have, as you said, blood tests and PET scans that can really, essentially, nail the diagnosis quite effectively in patients who have Alzheimer's disease. Now, it sometimes produces

indeterminate results, but most of the time, it's pretty accurate. And so we don't need to go back to lumbar punctures or spinal taps, the way we used to do five or 10 years ago.

NANCY KEACH: And I'm just going to bring this up because I've wanted to ask this to somebody, because we're doing a project at BrightFocus where we're actually going to film patients going through these tests as a service, so that people who are told, you have to go to get this, they can see what to expect, because this isn't really out there right now.

And so one of the people that we're in touch with– his name is Tim– told me he had had a lumbar puncture done three times. And he said it's not required. He's participating in the AHEAD study. He has had it done three times, not because it's required anymore, but because he gets so much more information from it. So, Dr. Newhouse, again, I'm putting you on the spot, but can you explain what additional types of information you could get from a spinal tap than the other tests? Or should I ask that on a different episode?

DR. PAUL NEWHOUSE: No, we can discuss that.

NANCY KEACH: OK.

DR. PAUL NEWHOUSE: So spinal fluid, of course, comes directly from the brain. And so it can give us additional fluids, additional proteins, additional molecules that are either hard to measure in blood or impossible to measure in blood. And so what it does is it gives us, essentially, something that's a bit closer to the flagpole, if you will, in terms of what the neurons, the nerve cells are actually doing.

And so he's correct that you can get additional information. At this point, it doesn't seem to be required to make the initial diagnosis. But as I think I mentioned to you the other day, we're actually starting a study where we're giving people two lumbar punctures over 12 weeks because we need to measure a molecule in the spinal fluid to see if our new drug that we're developing actually engages with the target.

And so sometimes you do need to get the spinal fluid, but that's kind of an early phase drug development kind of thing. In clinical practice, routine lumbar puncture isn't really done that often, unless there's some diagnostic question that we just can't answer with the other tests. We've done them, right?

NANCY KEACH: That's interesting.

DR. PAUL NEWHOUSE: And so if we have a patient with memory loss who has a

negative blood test and a negative PET scan, then maybe a lumbar puncture would be helpful in that case.

NANCY KEACH: And I'm going to put in a plug for them, because a lot of trialists will tell me that people most fear the lumbar puncture. But at the end of their assessment period, they'll say, gosh, the lumbar puncture wasn't so bad. It was that psychological testing that was really awful.

DR. PAUL NEWHOUSE: That's right. That's exactly right.

NANCY KEACH: Is that right?

DR. PAUL NEWHOUSE: People hate having their memory tested because, of course, it can make you feel bad to have your memory tested. We have such good techniques now with lumbar puncture, with spinal taps. We have much tinier needles than we used to do, used to use when I was in training. I used to do lumbar punctures with a big, fat needle. Nowadays, it's a tiny needle. And we, at Vanderbilt, are blessed with an absolutely wonderful neurologist who does all of our LPs for us. And she's amazing, and the patients love her. And she makes it a very smooth experience.

NANCY KEACH: Oh, that's wonderful to hear. I want to just respond to Richard's question about what is considered an early diagnosis of Alzheimer's. I want to mention, I think we've done two full episodes on getting an Alzheimer's diagnosis that are on the website at brightfocus.org/zoomin. So if you take a look at brightfocus.org/zoomin, and look at the two episodes about getting a diagnosis, I think that'll be really helpful to you.

And also, last month's episode with Dr. Suzanne Schindler about Alzheimer's blood tests was done within the last month and is very up to date on what the blood tests can tell you and when you should get a blood test.

DR. PAUL NEWHOUSE: And she one of the world's experts on that.

NANCY KEACH: Yeah, and a wonderful, generous person. So I think I talked briefly about the ADAGIO eligibility and that that's for psychosis. You mentioned ADEPT is looking at the effects of KarXT and agitation. And the last one, there's trials called MINDSET 1 and MINDSET 2. And the last time I downloaded, it said the age was 60 to 85 years to be eligible and that you do need a diagnosis of mild or moderate Alzheimer's dementia. And for those that are aware of what the MMSE is, your score of 12 to 22, inclusive.

So there are other criteria, but these trials are currently recruiting. So again, I know

our audience consists of a lot of people who want to participate in research, which is fantastic. So you can take a look at the trial finders. And if you do have questions, you can send them to us at BrightFocus Foundation. And we'll try to help you find out more information, or at least let you know how to find out the information.

Rebecca asked a really interesting question in the chat. She wrote, "How do you go about explaining clinical trials to a participant that is experiencing cognitive decline? And how do you obtain informed consent for participation from an Alzheimer's patient?" Can you give a high-level answer on that one?

DR. PAUL NEWHOUSE: Sure. I mean, this is a question that I've actually been involved in addressing at the systems level for decades and actually helped design criteria for this. And so one of the questions that always comes up is, well, but if a person has memory impairment, first of all, how can they understand that it's a clinical trial, and how can they consent to that?

So consent is not a black-and-white thing. It's not like you lose the ability to consent to things, and here you had it, and now you don't. It really is relevant to the particular thing that you're consenting for. And so I might be competent to consent to a trial, even if I'm not competent to manage my finances, for example. And so competency or ability to consent is really situation-specific. That's one thing to think about.

The other thing is that we want somebody to be able to understand that a trial is not normal clinical treatment. So there's normal clinical treatment that you can consent to, but then there's also experimental treatment or a clinical trial, which is not normal clinical treatment. And so a patient has to be able to understand that difference. And if they understand that difference, then they have the ability to then understand the procedures and the things that are involved. And so we believe that someone who has the ability to understand that is usually competent to consent.

Now, they don't have to necessarily always remember that they've consented. But memory loss by itself doesn't invalidate somebody's ability to consent to a trial. And that's generally been upheld by most states. Now, it is the case that in some states, we have something called a durable power of attorney for health care. And that can also help people.

And so I always recommend to my patients that they consider naming a DPA for themselves. And hopefully, they will have someone who can help them consent if they lose the ability to consent during a trial. And so many states offer DPAs. I have one with my wife. We both are DPA for each other, in case something happened to us. And so I always recommend that. And we use that, sometimes, in research.

NANCY KEACH: Thank you. Richard wrote in, who was asking about the diagnosis. And he's written "Actually, I've had Alzheimer's for about three years. On Leqembi and doing well. Interested in the possibility to add KarXT." First of all, I'm so glad you're doing well. And I'm so glad you are taking advantage of the drugs that are approved and showing results.

And Dr. Newhouse, you can correct me, also, if this is not correct. From what I read about these KarXT trials, currently, you would have had to have been off Leqembi or Kisunla for at least six months to be eligible for these trials. And actually, I think you were just saying this, Dr. Newhouse, that the way a drug is administered in a clinical trial is quite different than in the real world.

So the reason that you wouldn't take, at this moment, Leqembi and KarXT together, at this moment, is that that would befuddle the results of a trial and not make them clean, so to speak. So we're talking, I guess, again, about the possibility of adding KarXT to a monoclonal antibody in the future, but not today.

DR. PAUL NEWHOUSE: Yeah, I don't recall exactly what the restrictions are for each of these trials in terms of whether patients are allowed to be on things like Leqembi or Kisunla. I'm not exactly sure which trials allow it and which prohibit it in the KarXT trials. But the reality is that drugs like Leqembi and Kisunla are becoming standard of care. And once they're standard of care, you can't deny them to patients, even patients in a trial. And so the reality is it's not ethical. You can't tell somebody, oh, I'm sorry, you can't take that drug, even though it's standard of care. That just doesn't fly ethically. And so, we would allow and we are allowing concomitant Leqembi or Kisunla in certain trials.

NANCY KEACH: Ah.

DR. PAUL NEWHOUSE: Now, certain trials, we can't because we're doing either early phase, very early phase drug development, or something like that, where we worry about the overlap because we don't know what the drug interactions are between the two. I think that's less of an issue here with KarXT, to be honest with you, because the drug's been around so long. We know a lot about it. It's not a new molecule. It's been around 25 years. It just hasn't made it to market yet, until recently.

And so but to answer this gentleman's question, I wouldn't advocate adding KarXT unless there's a specific reason to do so at this point. And so, in my clinic, we would not be prescribing this even off label, unless there was a specific reason to do so– at least not yet, anyway.

NANCY KEACH: Not yet.

DR. PAUL NEWHOUSE: Yeah.

NANCY KEACH: Thank you for that. When we talked yesterday, when we were preparing, you were excited about the results of a study called the LiBBY study. So I'd love for you to talk a little bit about that or any other studies that you're excited about, that have shown to help in any either of these indications, agitation, delusions, or actually, changing in cognition.

DR. PAUL NEWHOUSE: Right. So the LiBBY trial was a very unusual and interesting study, which was trying to relieve agitation at the end of life. And there, Amanda's posted the study website there for everybody who's interested in. And it was using THC, which is the active ingredient in marijuana, plus cannabidiol, which is another derivative of the marijuana plant. And so this combination was used in oil, actually. It was an oil. And it was given to patients in hospice, hospice-eligible patients at near the end of their life to relieve the terrible distress that can sometimes occur in patients in their last phase of this disease. And the results have been quite impressive. And so they were presented this summer at the Alzheimer's International Conference. They're going to be presented again in a few weeks at the Clinical Trials in Alzheimer's Disease. And there's a manuscript in preparation for this.

So we're very excited about the results of the LiBBY trial. We participated in this trial here at Vanderbilt. Dr. Jacobo Mintzer was the principal investigator of the national study. And he's done a wonderful job in bringing this treatment forward. Now, it's a controversial treatment, let's be real. It's THC and cannabidiol, which are federally restricted substances. And so I think we're a long way from getting this to the clinical market yet.

And I think there are more studies that are on the drawing boards, getting ready to expand this to maybe people who are not hospice eligible. Could it be helpful for agitation, even in patients at earlier stages of the disease? But it's been a very positive readout from the trial, quite impressive data. And we're excited.

NANCY KEACH: I think that's fascinating. And I have a couple questions. When you talked about people being in a lot of distress at end of life– I'm assuming you're talking specifically about people with Alzheimer's or other dementias– are you talking about physical pain? Psychological pain? Both? Where do you see the benefits that are shown in the LiBBY study?

DR. PAUL NEWHOUSE: Well, I mean, here's the problem, Nancy. At the end of life, one

can't really even distinguish between the two. So physical distress, emotional distress, pain, all of those wrapped together may produce dramatic agitation at the end of life. And the drugs we've had previously to control this have been very poor– morphine, for example.

NANCY KEACH: Oh.

DR. PAUL NEWHOUSE: When my mother was dying from Parkinson's disease, they wanted to give her a lot of morphine and sedate her. Well, that's not very helpful. And so I think drugs which are more specifically designed to cool the fires, as it were, of the emotional system might be very, very helpful. And it looks like, preliminarily, at least, that this combination of medications of THC and cannabidiol can do that.

NANCY KEACH: And I've talked to Dr. Jeff Cummings about this because he's the clinical trial guru and overseeing how many clinical trials are happening in Alzheimer's and 182 drugs. And there's almost nothing being tested for people in moderate or later stages of these diseases. And the field is very excited about can we stop it, or can we slow the progression? Can we catch it early before it starts? But there's millions of people who are in moderate or later stages. And so it's actually really encouraging for me to hear about testing to try to help this population.

DR. PAUL NEWHOUSE: That's right. Because we already know, for example, that drugs like Leqembi and Kisunla don't seem to be very helpful to people in moderate and late-stage disease. And so, the emphasis– oh, well, go earlier, go earlier, go earlier. But as you said, people are still going to get this disease, and they're still going to suffer the symptoms.

So we need new symptomatic treatments like KarXT, like THC and cannabidiol, like other things as well that may be helpful in improving the function of what brain systems are still there for us to influence. And the brain still retains some ability to respond to these treatments, even in late-stage disease, as we can see with the LiBBY trial.

NANCY KEACH: That's incredible. Are there any other medications or interventions that you think are promising in that area?

DR. PAUL NEWHOUSE: So we're starting the testing of a molecule that affects the inflammation that occurs in the brain, or the oxidative stress that occurs in the brain, as a result of things like amyloid and tau. So amyloid and tau are the driving protein problems, but they spin off a whole host of all sorts of other nasty processes. Inflammation would be one of them.

So when you and I get an injury, we get inflammation. When we get an infection, we get inflammation. And if that doesn't stop, if that gets out of control, it becomes its own problem. And so what we're testing is a molecule that we think will actually act like a molecular sponge to soak up all of these nasty byproducts that can damage other cell systems. So we're going to be testing that this year.

We're also investigating drugs, even, like nicotine, which is another cholinergic agonist. We know it has a notorious reputation because it's connected to smoking and tobacco. But nicotine actually has direct molecular effects on the brain, and it affects attention and memory and, perhaps, emotional regulation as well. And so we're also testing that. We hope to have the results of the MIND trial published here relatively soon. And we're excited for that work as well.

So like you said, we have to develop treatments for everybody who doesn't necessarily stay smoothly stable on Kisunla or Leqembi. And that's going to be most of us who develop this disease. And so we have to have, as one of my former colleagues used to say, multiple shots on goal. We have to really think of this as a multi-focal disease and a multimodal treatment approach.

NANCY KEACH: Absolutely. This is not necessarily a question you might want to answer and address, but I thought it was a really interesting question because it's from somebody who clearly has a disease. It's from Michaela in Reno, Nevada. And she wrote, "How do you deal with people who don't understand what I am going through? How to explain to them what it's like for me?" And I wondered if you have insight, because you do work with patients who are experiencing dementias, if you have any thoughts about this. Especially if someone is having delusion or agitation, how do they explain to people what they're feeling like?

DR. PAUL NEWHOUSE: Yeah. Well, it's a profound question, Michaela. And I can appreciate it can be very, very difficult. It's not always possible for everyone to understand what that's like. It's hard to put ourselves in the shoes of someone whose brain isn't functioning as well as it used to. I think just asking for understanding and asking people to realize that if I don't remember that you called me yesterday, that's not because I'm trying to ignore you, but because my memory isn't as sharp as it used to be, and here's the reason why. And I'm getting treatment for that, or I'm dealing with that.

And I think most people will be compassionate about that, most people who care about you. We're far from the days that, for example, when Rita Hayworth, the famous Hollywood actress, had early onset Alzheimer's disease, and people thought she was

just drunk or alcoholic or something like that. And so I think we've come a long way since there. Alzheimer's disease wasn't well-known. Even during my medical training, it was thought to be a, quote, "rare disease." But now we know that's nonsense. And so I think people will be understanding.

NANCY KEACH: I'm glad you brought that up, because as I said, I've been in this field since 2009. And around 2014, some films started to come out. Still Alice came out. My husband did a film called Glen Campbell– I'll Be Me. And there have been many films that have come out since then, some that we've done, and then, I hope, programs like this one that are starting to normalize the conversations and also help everybody understand what people are experiencing.

I think probably not a day goes by that I don't say to somebody who's talking about their frustrations with someone who has a dementia, well, I'll say they're not asking you the question repeatedly on purpose. Just don't get upset. This is a condition. This is something that's actually happening in the brain. And so I think the more we repeat that publicly and the more we continue to show the disease as something that literally millions and millions of people are experiencing, the better. So hopefully, we're all having a piece in that, and you especially by doing the work that you're doing, Dr. Newhouse. So thank you for that.

And I'll say, as our time today comes to a close, I want to thank my wonderful colleagues at BrightFocus Foundation, Dr. Sharyn Rossi, who's been answering some of your questions in the chat; producers Amanda Russell and Alexa Villarreal; the team at M Squared, who are hosting us on this platform; and again, especially thank you, Dr. Newhouse, while your power is out at home, for running over to your son's and not canceling our episodes. So we really appreciate your time and expertise today.

DR. PAUL NEWHOUSE: All right. Well, thank you for having me, Nancy. And thank you to the wonderful team you have.

NANCY KEACH: Thank you. And just to close, if you have questions that weren't answered today, there are 48 episodes of Zoom In online at BrightFocus.org/zoomin. Or on YouTube, you can find them. They're available for free. We have a bunch of other resources that are available for free that are on our screen, including this wonderful FDA-approved Alzheimer's therapies infographic in English and Spanish.

If this program was helpful to you today, please share the link with at least three friends, brightfocus.org/zoomin. We'd love for you to help amplify what we're doing and promote us. We also have now turned this show into a podcast that is audio and video. And that is called Let's Talk Alzheimer's. So go take a look at Let's Talk Alzheimer's.

Our next episode on November 5 is going to be something we've never addressed and I think will be really interesting. And the reason we're doing this now came out of our discussion with Dr. Suzanne Schindler on blood-based biomarkers. But we're having a program on November 5 with Jalayne Arias, "Alzheimer's Blood Biomarker and Genetic Tests: Legal and Ethical Considerations." So I think that's going to be really interesting and invite you all to participate.

And I want to say, as I always do to all of you, thank you for participating. You are not alone. We are here for you. And a lot of other people are going through what you're going through. And I don't always say this, but also, there are just so many incredible researchers like Dr. Newhouse who have this disease in their family, who have devoted their lives to trying to make a difference. And we've come far in the last decade, and we're going a lot farther now, which is incredibly encouraging.

So you're not alone. And just always remember, life is very short. Tell everyone you love how much you love them. Give them a hug. Keep them close to you. Thanks, again, to everyone for joining us. We look forward to seeing you again soon on November 5. Be well.

Resources:

- BrightFocus Clinical Trial Finder: https://brightfocus.org/clinicaltrials
- Bristol Myers Squibb also provides trial information at: www.bmsclinicaltrials.com or by telephone at 855-907-3286