

Agitation in Alzheimer's Dementia

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

NANCY KEACH: Welcome everybody. From BrightFocus Foundation's Alzheimer's Disease Research Program, I'm Nancy Keach. Welcome to the 44th episode of Zoom In on Dementia & Alzheimer's. This program is generously sponsored by Lilly, Biogen, Eisai, Genentech, and Axxome Therapeutics. And we are deeply grateful to these sponsors for making these free programs possible.

Today's program is Agitation in Alzheimer's Dementia. And we're going to talk about what agitation is, what it isn't, what the triggers for agitation are, and how to manage it. And I am absolutely delighted to introduce today's guest expert who's come away from the Curaçao / Côte d'Ivoire game to do our program. And that's why he's in his jersey instead of his medical outfit.

Dr. Brent Forester is the chair of psychiatry at Tufts University School of Medicine and psychiatrist in chief and chairman for the department of psychiatry at Tufts Medical Center. Prior, he spent a quarter century of his professional career in leading roles at McLean Hospital and Mass General Brigham. Dr. Forester is an expert in geriatric psychiatry, specializing in the treatment of older adults with depression, bipolar disorder, and behavioral complications of Alzheimer's disease and related dementias. His research focuses on novel treatment approaches to manage the disabling behavioral complications of dementia, such as agitation and aggression. Welcome, Dr. Forester. Thank you for stepping away from the game for us.

DR. BRENT FORESTER: It's a pleasure to be here, Nancy, and everyone.

NANCY KEACH: Really delighted to have you. And I found that the over 150 questions we received today were really kind of heartbreaking. And so I'm going to try to fit a lot into this hour. There's a wide spectrum of behavioral and psychological symptoms or

neuropsychiatric symptoms that people describe that accompany Alzheimer's-related dementia. There's wandering and sundowning and anxiety, confusion, aggressive behavior, delirium, hallucinations. So my first question to set the stage is, how is Alzheimer's agitation defined? How do you discern what we call agitation from other neuropsychiatric symptoms?

DR. BRENT FORESTER: Thank you, Nancy. And I just want to thank you all again for being here and for being invited to speak with you today. I've been in this field for about three decades, and my passion, for whatever reason, has turned out to be exactly this topic. And one of the reasons I was drawn to this is because as you all know who are here today and by reading all of your questions, Alzheimer's disease and related dementias is not a disease that impacts the individual with the illness, it really is a family disease. And there's nothing more disabling about this illness than these behavioral and psychological symptoms. Because as you all know, the care partners of people with dementia become overwhelmed and exhausted with care giving not because of memory loss, but because of the symptoms you just described, Nancy. And they're confusing to families to understand what they're all about. They're confusing for clinicians sometimes who are not really, truly expert in this illness, like primary care clinicians or even my colleagues in general psychiatry who don't do this work all the time to understand what these symptoms are all about.

So the first is actually exactly what you said, the definition. So one of the problems is when you read our literature, you're going to read lots of different names for the syndrome that Nancy's talking about. Some people call this the behavioral and psychological symptoms of dementia or BPSD. Other groups are now talking about the neuropsychiatric symptoms of dementia. So there are a whole number of acronyms that are used, but at the end of the day, these symptoms represent a whole range of symptoms that are common over the course of this illness. It could be early stages of apathy, which is lack of motivation and anxiety and depression, or as the disease progresses, agitation, aggression, paranoia, hallucinations. But I think most importantly, is that when you, as a care partner, have a loved one with any of these symptoms, you try to do the best you can in describing what it is that you're observing.

So, for example, agitation. What is that? It's been broken down into two types. There's the verbal type and there's the physical type. It could be yelling and screaming, or it could be pacing and wandering or hitting or biting. And then there's probably a continuum where it moves into what's more, aggression. And so this agitation, aggression exists a bit on a continuum, and we actually have rating scales that can allow us to define the prevalence and the severity of these symptoms. So we can actually measure whatever the intervention is going to be to see if it's effective. So as

we go through this discussion, hopefully, we can get into more about the causes, the evaluation, the treatment. But I could go on and on about defining each one of those.

And the last thing I'll say is the International Psychogeriatrics Association (IPA) has convened a task force in four different areas of this larger syndrome to try to really understand this question, how do we define it? What's the impact of it? And how do we evaluate it and treat it? And the four areas include apathy, which is lack of interest or motivation. Agitation, which we just talked about. Depression. And then this umbrella term psychosis, which includes paranoia or hallucinations. So there's a lot going on right now in the field to identify and define and thereby come up with better targeted treatments for these very disabling symptoms.

NANCY KEACH: That's so interesting. The next question I was going to ask you was, can agitation be measured? Someone wrote in and said, "Are there standardized tests to measure behavioral impairment? For example, I saw mild behavioral impairment referenced in an article versus an MCI initial diagnosis." So actually, you answered it for me. It can be measured. Do you only use those measurements when you're, say, running a clinical trial, to see if something is efficacious, or would there be a reason to try to measure someone's agitation just broadly?

DR. BRENT FORESTER: So Nancy, another amazing question. I would say as a clinician, because I spent a decade to 12 years of my career only taking care of patients and teaching. Research then grew on me, and I started doing a lot of it as we'll talk more about. And now I do both. And my main clinical practice is in the assisted living memory care world, where I see a lot of people who are now in moderate and advanced stages of illness, where families really can't manage their care anymore, and they're getting holistic, expert care, and treatment.

But one of the things that I have noticed since I've done both clinical work and research, is that the research instruments that allow us to objectively measure agitation, like the very simple four item Pittsburgh Agitation Scale or the Neuropsychiatric Inventory or the Cohen-Mansfield Agitation Inventory, those are three that we commonly use. They're wonderful instruments in research to measure severity of symptoms and to track improvement over time or worsening, for that matter. But they're very hard to employ in clinical practice. The Pittsburgh Agitation Scale may be the easiest because it's four questions, and it can be done once a day or even more than once a day, and it's based on observation of the patient. Some of them require an interview with a care partner, which may not be available in a routine clinical setting, but should be. And some are a composite where you put the observation of the person with the illness and the care partner's impression of what's going on together into one

number.

I would love us to find a way to take some of the measures that we have, and find a way to collect this data, if you will, in a remote sort of fashion. Because if I in a clinical practice setting, ask a nurse or a family member to fill this out every time I see somebody, that's very much one point in time. And those of you who are on this call know that these symptoms wax and wane over time. They fluctuate. They happen in the morning or late in the day or at night. Or maybe they're gone for three days, then they're back again. It's a moving target. And so it becomes very hard to use, like a one-point in time measure or someone's recollection of the past week or two to really do a thorough job of assessment. But I think that's where the field is going to go, whether it's the wearable devices or other ways to track and collect this information in real time, that will help us so much more in understanding how effective our behavioral and our pharmacological interventions are.

NANCY KEACH: Thank you. Joseph from Holly Ridge, North Carolina, wrote in, "What is the percentage of Alzheimer's patients who develop agitation?" And Terry wrote, "Is agitation inevitable for the person with AD? So if you're diagnosed with Alzheimer's, you're definitely going to become agitated. And what percentage of people end up with this?"

DR. BRENT FORESTER: So if you put all of those vast array of symptoms we first talked about that are agitation plus depression or paranoia or hallucinations, if you add all of those together, over the course of this illness, it is way more likely than not. Well over 90% of people with dementia at some point during the illness will have one or more of those symptoms. Agitation itself is probably in the 40% to 60% range in terms of prevalence over the course of the illness, depending on what study you look at. But that number is not as helpful as understanding what may precipitate it and what may prevent it from happening. But I would say, somewhere between 40% and 60% depending on the studies you look at.

NANCY KEACH: And Rose's question, "Is agitation associated with any particular stage of Alzheimer's?" And a lot of people ask this question.

DR. BRENT FORESTER: Clinically, we see this and research would bear it out as well, that as people progress from very mild to more in the moderate stage, where people start having more difficulty with not just their independent activities of daily living, like driving and paying the bills, but also some ability to care for oneself, that's when we start seeing a much greater prevalence of agitation, less so in the very early mild stages. But it really can occur at any stage. But I think of agitation being more common

and frankly, more severe as the illness progresses in the moderate and more advanced stages.

NANCY KEACH: And is agitation different in different types of dementias? I have Richard from Belleville, Illinois, "Is agitation an issue equally possible with Alzheimer's and other forms of dementia?" And Harlene from Oakland, California, "Are there differences in agitation specific to Alzheimer's, Parkinson's, other dementias?"

DR. BRENT FORESTER: Another amazing question. The way I think about this is that each one of those types of dementias have certain psychiatric symptoms that are more or less common and are likely related to where in the brain the changes are happening, where the death of brain cells are occurring, or disruption in brain pathways are occurring, and the type of illness it is.

So I'll give you an example. In the Lewy body type of dementia, we often will see patients, individuals with dementia of Lewy body type who not only have symptoms that look like Parkinson's disease, like tremor, and difficulty with shuffling gait and prone to falling and reduced facial expression, but also will develop these visual hallucinations that are described often as animals outside the window, or babies on the couch, or very clearly describing things that the person is seeing. And interestingly enough, those hallucinations are not always associated with worry or agitation in the person who is describing them. Sometimes they're described as matter of fact, but those hallucinations are common in Lewy body dementia. They can happen in other forms of dementia. Whereas agitation is common in all dementias. And I think in Lewy body, sometimes it's related to the hallucinations.

In Alzheimer's disease, it may be related to the brain changes that are happening in certain parts of the brain. Or we'll talk more about cause. I don't think of agitation as being specific to one form of dementia or another, but what's most important is really trying to understand what is causing it in the moment. And that really is the key to figuring out how best to prevent it and to treat it.

NANCY KEACH: Well, you've brought me beautifully into the next question. Vivian wrote, "Can a urinary tract infection, UTI, cause behavior changes?" And the overarching question I wanted to ask was, what are the triggers? What are the triggers and causes?

DR. BRENT FORESTER: So can I tell a little personal story that's happening as we speak?

NANCY KEACH: Yes, sir.

DR. BRENT FORESTER: Half an hour ago, I got a video FaceTime call from my sister and my mother's aide. My mom is 84. She has what I would believe is mild vascular dementia. She lives in an independent senior living community with 24/7 care because she needs a lot of help with ADLs (Activities of Daily Living). And four days ago, she started having difficulty with expressive language and inability to remember or be able to say our names, her three kids. And was off on the day. That's not like her. I mean, she has mild dementia, executive dysfunction, like decision-making, planning, some delayed recall, but not that kind of confusion and disorientation. And sure enough, she had a urinary tract infection. Now, her symptom was confusion. It was not agitation, thankfully, but agitation, seeing things that aren't there, irritability, and confusion are really, really common in people who develop urine infections. They're frankly really common in people who are older, with dementia, who develop any kind of medical problem. And so that's what I will talk about now, which is that-- and by the way, she's doing a little bit better.

NANCY KEACH: Good.

DR. BRENT FORESTER: She's going on oral antibiotics in the next hour and hopefully going home later today. So I feel your pain in terms of how hard this illness is. And we can get into that aspect of caring and how hard this is, but I will say personally, it's taken a physical and emotional toll on me in a way that having done this work clinically for 30 years, I could never have truly appreciated until you're experiencing it yourself.

So anyway, the way I think about agitation as a symptom is to try to figure out what's driving that symptom. So whether it's yelling and screaming or irritability or biting people or wandering or pacing, I think about it being caused by three buckets of problems. One is, what's going on in the environment?

So you know that if you've got a loved one with dementia, who is repeating themselves over and over again and you're getting frustrated and you may be getting the same questions five times an hour, much less five times a day. And you may get irritated yourself. And so the way in which you speak with your loved one with dementia may actually trigger them, and they get cranky and irritable with you. So that's an environmental trigger. The time of day could be an environmental trigger. As the sun goes down, our circadian rhythms are impacted. And it's more likely that the agitation is going to come on late day, early evening as the light changes. Or if you're in a long term care facility and there's a change of shift and there's a lot of commotion and noise, or if you've changed to it, you go from home to a hospital because you've got a delirium. All of these things can trigger agitation. And so when we come up with a plan for treatment, we have to take all of these into effect. So that's one bucket is, what's

going on around the person?

The second bucket are medical causes. So urine infections happen to be just really common in older people, women and men, but especially in women. So I don't know if there's something really special about a urine infection that goes directly to your brain and causes these changes. I've never understood that. Honestly, I've never talked to anyone who truly understands that because it could be any infection. I'll just keep using my mom as an example. I could use 100 patients I've seen in the last how many years. But two months ago, my mom developed confusion and agitation. And she had COVID pneumonia. And when the pandemic hit, we saw a lot of older adults with dementia develop confusion and delirium and agitation as their first symptom of an infection, before they had a fever and a cough. So any infection can do this. Change in blood sugar can do this. Low oxygen from emphysema could do this. Heart disease that's not stable can do this.

Really important, though, is to be aware of changes in medication. Older adults are very, very sensitive to medications. Side effects of medications can cause agitation. If you've been on a medicine for 5 or 10 years at the same dose and now you have agitation, it's probably not that stable dose of medication. But if it's been a change in the last week or two or the dose was increased, that's something that the doctor should be aware of. And then there's the over-the-counter stuff that people take all the time. When I give talks often to groups like this, and I'm not going to do it today. But a lot of people take Tylenol PM as an example, as an over-the-counter medication to help them sleep at night. Which one or two doses is probably fine. But as your brain ages, but especially with dementia, you're sensitive to the anticholinergic effects of the Benadryl that's in the Tylenol PM, and that can cause agitation and confusion and delirium. So the list goes on and on. Constipation, pain, sleep deprivation, all of these things can cause agitation.

And then the third bucket is some of our loved ones and our patients, our family members have a history of psychiatric problems earlier in life. They've had recurrent depression since their seconds, or they've had mania before, or they've had psychosis. And now they're older with dementia, they can still have a recurrent episode. So the agitation could be the sign of a recurrent episode of a psychiatric problem. That's not a new problem. It's just coming back again in the setting of dementia. And sometimes, a person with a pre-existing psychiatric illness who now has agitation and confusion, it could be a recurrence of their previous illness. It could be a new medical problem. It could be what's going on in the environment. And very often, it could be all three, which is why the comprehensive assessment of the cause is really the key thing to finding out the right treatment.

The last thing I'll say is, the fourth bucket, if you will, would be what exactly is going on in the brain with someone with dementia, even when they don't have a urine infection or they're not on a new medication causing a side effect? And what's going on is in Alzheimer's disease, as an example, there's a buildup of amyloid plaques and neurofibrillary tangles, and these abnormal protein deposits are causing an inflammatory response, and they're causing eventually death of brain cells and disruption in the different pathways in the brain where the different parts of the brain talk to one another and neurotransmitters are changing. And all of these brain changes due to the dementia can also elicit the signs of agitation. I know that was a long answer, but hopefully it was helpful kind of background.

NANCY KEACH: No, it's very helpful. And what I'm going to do because I have so many questions, but most people are really writing about what they can do and how to react in a situation. So I'm going to start to try to spend the rest of the time we have talking about intervening and how to manage. And get to some of the 20 questions in the chat already in the 150 that were sent ahead of time.

So let's start to talk about management strategies and people's experiences. And let's start with non-pharmacological. And then I want to get into the medicine area because there's a new treatment that's been approved and that's exciting. And there are other things that are approved. So Judy from Emory, Texas, wrote in, "Can you talk about how keeping things consistent sleep, calm, and quiet might help reduce agitation and irritability in Alzheimer's? We've seen those three make a real difference in lowering reactivity. So I'm curious if the research lines up with that." So just to get us started on non-pharma.

DR. BRENT FORESTER: So the non-pharmacological interventions and I can list a few, the rule is, this is what we do first. We always think about prior to medication, what can we do about someone's environment or the way they're leading their life, their lifestyle? What types of interventions in that domain can help? And even if we do wind up intervening with medications or other treatments, those non-pharmacological interventions should be the rule for everyone.

Sleep is so important because when people are sleep deprived, their brains are more sensitive to changes that are going on around them. They're more sensitive to pain, noise, and the effects of anxiety. Agitation is more common in people who are sleep deprived. So assuring effective sleep and excluding and treating, if it's discovered, sleep disorders that can be impacting sleep like obstructive sleep apnea, restless legs syndrome, all of that is really important.

A regular diet is critical. We know that there are some amazing studies that have looked at the beneficial effects of different kinds of dietary interventions on healthy brain aging. Not only may it help cognition and function, but we know it helps mood and behavior too. So principles of the Mediterranean diet, the MIND diet, those types of things can really be effective not just for cognition and function, but also for these behavioral symptoms like agitation.

I think exercise may be one of the best studied interventions for healthy brain aging. And not only may it help with reducing inflammation and reducing some of the bad consequences of oxidative stress in the brain that can damage brain cells, but it really does reduce stress. It really does reduce. I mean, think about all of you. If you exercise regularly, you feel better. You just feel better. The exercise doesn't have to be training for a marathon. It could be walking. And if you can't walk, it could be a stationary bike. Engaging the body in that way helps the mind in so many ways.

The other thing in terms of the basics is distracting someone from whatever they're worried or focused on that may be triggering or causing the agitation and trying to know. And again, this is where it can't be prescriptive. Like this one thing works for all. That never works. It really has to be very individualized. But what does the person love to do? What normally keeps them calm? Is it talking about the past? Is it listening to music? Is it going on walks? Is it a pet? Some people are deathly afraid of dogs. Others love dogs and get calm around dogs. So you have to know for the person who is experiencing the agitation, what is it that helps keep them calm?

So all of that is really important. I'm involved with a group that's actually doing a review of the literally thousands of studies that have been done in this area, and I just saw the summary of some of the analyzes that are being done. And the bottom line is that despite all of this research, there is no one golden rule here or one magic bullet. It really is holistic and comprehensive and individualized. But some areas do seem to have more evidence. For example, music. There's a lot of research on the beneficial impact of music therapy, if you will, for people with agitation. That does seem to help. That may have the strongest evidence, that may have the most studies with the strongest evidence of all the things that this group looked at. But again, the list goes on and on. I think the bottom line here is being very individualized, being creative as to the solution, to make sure that you understand the environmental circumstances that might be triggering to use some of the basics of healthy brain aging like we talked about with nutrition, sleep, exercise, et cetera. And no matter what we do with medicines, all of those non-pharmacological interventions need to be utilized.

NANCY KEACH: So before I get to medicine, and I think the fact that there's a lot of

evidence on music is extraordinary, and I think we have to do a whole episode on music and the brain. Having worked on the documentary, Glen Campbell, I'll Be Me and watching how different he was when he was singing or performing, he would just come to life and then not be able to count driveway gravel in his hand afterward. It's fascinating.

But I'm going to throw some other things at you that people wrote in about and then go to the medicines. CBD and cannabinoids, pulsed electromagnetic field therapy, Robert from Oroville, California had wrote, "Does 800 milligrams of curcumin with black pepper daily and/or 40 hertz light and sound therapy reduce agitation?" So a bunch of questions about other types of non-drug interventions. Although I guess you could call CBD a drug.

DR. BRENT FORESTER: Yeah, CBD and any cannabinoid is a drug. And curcumin and other products like that are often categorized as nutraceuticals or vitamins. But nutraceuticals essentially, that are not FDA approved for anything you can buy over the counter. So let me just take them one at a time. And then the third, I would bucket into something called neuromodulation.

So for CBD and THC. So cannabinoids. I have been involved in working with cannabinoids in research for about 20 years and recently completed a trial I'll tell you about. But cannabinoids are now available in many different formulations, and this is part of the problem. So the potential benefit of cannabinoids for agitation as an example are biologically that they do seem to help with the neurotransmitters that we know need to be modulated to reduce anxiety and agitation and elevate mood. So we know that there's a neurotransmitter effect of these cannabinoids. We also know that they may have other more basic biological effects that could be helpful for a brain that's suffering from the symptoms and the disease of Alzheimer's or other dementias. And what it's doing biologically is reducing inflammation. That's always a good thing. Usually, always a good thing. It helps to promote blood flow. Cannabinoids may help to reduce the damaging effects of what we call oxidative stress from these free radicals in the brain that are basically damaging brain cells. There's a lot of biological plausible reasons why cannabinoids may be helpful. The problem is, whether it's CBD, which is a type of cannabinoid called cannabidiol, or whether it's THC, which is the active ingredient in marijuana, which is tetrahydrocannabinol.

Now, in most states, they're available as medicinal therapies, and you can get a prescription to get them. And in many states, they're available in dispensaries for anyone to go walk in and get them. And the biggest problem is that they're completely understudied. We don't know enough about their drug interactions. We don't know

enough about their side effect profile. We really don't know enough about how effective they are for agitation. But most importantly, there are other compounds when you go into a dispensary and what you're buying beyond the THC or CBD. There are other types of cannabinoids that have other effects that are completely unknown. And so the research will never catch up to what's happening in clinical practice or in people just doing what they do.

So having said all of that, if there is a cannabinoid product that's been studied and we know the right dose and we know the drug interactions and we know the outcomes, safety, and how effective it is, then maybe we should think about it. So we just completed-- my colleague Paul Rosenberg and I at Hopkins and I've been at Tufts. And then prior to that, Harvard, we did a study over the last seven years studying a synthetic THC compound called dronabinol or Marinol. Marinol was approved in 1985 by the FDA. This is a great example of repurposing an old drug. This drug was developed by pharmaceutical companies back then to treat two things, to stimulate appetite in people who were suffering from HIV/AIDS, to stimulate appetite and help with weight gain. And it was also approved to reduce nausea and vomiting in people getting chemotherapy for cancer.

So because it was on the market, we got permission from the FDA and from the Investigational Review Board to use it in people with agitation and Alzheimer's. So we started using it clinically in collecting data. And then we got a grant from the National Institute of Aging to study it in a randomized trial. And we just completed the trial and published our results within the last year. And we found that indeed, on one of those measures I talked about before the Pittsburgh Agitation Scale, we reduced agitation over three weeks at a dose of 5 milligrams twice a day. We added it to whatever else people were taking so they could have been on antidepressants or anxiety medicines or other things. It was not monotherapy, but there is a signal that it does help and it was extraordinarily safe. People did not stop it because of severe adverse events, and we didn't see a worsening of cognition because of it. But again, it was only three weeks. It was only 75 people. And we just submitted a grant to try to do a bigger study. But that's the kind of rigorous research we need to really know if any of these things are going to work. So I will just say the cannabinoid story is a complicated one.

NANCY KEACH: Dr. Forester, what was the name of that?

DR. BRENT FORESTER: Yeah, the generic name is called dronabinol. The other name is the brand name, which is easier to remember Marinol. So that medication, again, you could get a prescription from a physician. It's prescription medication. You can't buy it over the counter. In Canada, they have a similar product called nabilone, that

I do believe now is here in the United States, too. It wasn't at the time we started the trial, which has been studied by my colleague, Dr. Krista Lanctot at Toronto, and that also helps with agitation and dementia. So there's increasing evidence that these cannabinoids may have an effect, but I would go with standard prescribed cannabinoids where there's data than walking into a dispensary and asking someone, what do you think would help agitation in my mom with dementia? They may come up with something, and you may want to try it, but make sure the doctors know what you're doing. So that's cannabinoids. OK. The curcumin, we could go on and on with the number of nutraceuticals that have been looked at, studied, people have wondered about for agitation or for enhancing cognition and function in people with dementia. Curcumin, omega-3 fatty acids, nicotinamide riboside we just finished a study on. That's a vitamin B3 compound. And the list goes on and on and on.

And all I would say with this is that the last time I saw any kind of report from a federal agency about this was about a decade ago. And nobody really felt at that time there was any definitive proof to suggest one over the other. And a lot of companies are marketing this heavily mostly for overall brain function, not for agitation in particular. So could it work? Maybe. Most importantly to know is that these nutraceuticals, even though they don't require a prescription aren't always without side effects. And they often have drug interactions that you need to worry about.

NANCY KEACH: And I want to reiterate that you just said there is not any scientific evidence that they are of benefit.

DR. BRENT FORESTER: Exactly. I don't recommend these types of treatments for agitation. If patients and families come to me with questions just like this question, I have a conversation just like this. And if they really want to try it, and I look it up and make sure it's not going to cause an interaction with other medicines they're on, then we could try it. It's just the downside at that point is it's just costly. That's all. It's a multi-billion dollar industry.

NANCY KEACH: My mom is 96 with MCI and she is up at night seeing those ads for every kind of nutraceutical in the world. And my sister has to go and stop her from buying them. So I know this is a very common situation.

DR. BRENT FORESTER: Very common. The third bucket is what I would call neuromodulation. So there are a number of different interventions now that are being used in people with depression and dementia or anxiety or agitation and dementia that are stimulation devices, if you will. So there's transcranial direct current stimulation, TDCS. Some people are looking at transcranial magnetic stimulation or TMS. I'm not

sure I was familiar with the exact product or methodology that this question had. There's another group at MGH and elsewhere that are looking at photobiomodulation. Basically, the effect of photons directly through the eyes into the brain that might actually have effects on cognition, function, and perhaps on behavior. I would say all of this is really interesting, and possibly one day will be helpful. But the research is in its infancy I would say it's in its infancy honestly.

NANCY KEACH: Let's talk about what has been shown to work and some of the medications. I know that there are some that have been previously approved, and then one that was just approved in 2026. Can you talk about the different types of approved medications?

DR. BRENT FORESTER: So I'll talk about the two that are approved. But just for context, for decades-- well, again, my career 30 plus years. So I've been involved in treating these types of problems for 30 years. And up until a few years ago, every single medication that I prescribed for agitation and Alzheimer's or for depression and Alzheimer's or for psychosis in Lewy body dementia, all of it was what I would call off label treatment, meaning the FDA never put their stamp of approval like this works and it's safe. And there was nothing wrong with that. But families needed to know that we were repurposing a medicine with limited information and no stamp of approval from the FDA for symptoms that were debilitating.

And so the largest, I would say, the class that's gotten the most attention, both for good and for bad, are the anti-psychotic medications. These medications have been around since 1954, when chlorpromazine, or Thorazine, was invented, which, by the way, really revolutionized the treatment of schizophrenia and other psychiatric conditions. Those older antipsychotics caused a lot of side effects, like Parkinsonism, and a movement disorder called tardive dyskinesia, and could make people dizzy with standing and all sorts of side effects. But they calm people down. They also were over utilized, and it led to a lot of federal regulations around the use of the entire class in long-term care nursing home settings. Not in my outpatient clinic, not in your assisted memory care facility, but in nursing homes starting in 1987. And those guidelines kept getting updated and updated.

And I think they're important because they make clinicians take a step back and do the full assessment we just talked about before using them. It doesn't mean you can't use them, you just have to do the assessment. And then every four months or six months or whatever the regulation is at the time have to justify why they're still needed. So we put into place a lot of regulation in nursing homes only, by the way, to make sure these were not overprescribed because the side effects can be problematic.

The newer generation, although it's amazing to think they're newer generation, the atypical antipsychotics also work on dopamine, but are generally safer from a movement disorder standpoint, like less Parkinsonism. Those medicines started to become available in the '90s with risperidone. Clozapine was the first in 1988, but risperidone or Risperdal. Olanzapine, Zyprexa, or quetiapine, Seroquel. Those three are the most commonly used. And another one, aripiprazole -- all were well studied. They were well studied in the '90s and early 2000s for agitation in dementia, for psychosis and dementia, but none of them ever got approval. And the reason they didn't get approved was not because they didn't work. They didn't get approved because of safety concerns. And the safety concerns included a risk for stroke and a risk for mortality.

The FDA did a meta analysis in 2005, and they found that in people on antipsychotics with dementia for agitation versus people with dementia and agitation, not on antipsychotics, there's a higher death rate over a period of a relatively short period of time in these trials of 6 to 12 weeks. That led to what we called a boxed warning. So if you were to look up any of the medicines I just mentioned, olanzapine, you would see, on the internet, a big box saying, warning, don't use this unless you've tried other things because it might cause mortality. The relative risk of death is small, but in the sample they looked at, which was pooling data from 17 studies, it was statistically significant. So every time that I've prescribed over the decades one of those medicines, I tell families, it may really help mom calm down. It may improve quality of life. And you also need to know there's a slightly increased risk of death. And this is the risk. And I've never had a family member say, don't prescribe it because of that risk, because the relative risks and benefits at that point, when you've got psychosis with agitation, you're like, we need something now.

That warning that came out in 2005, unfortunately it almost completely stopped research in this area for 20 years. It's a real problem. Almost 20 years. The first medication to get an approval for agitation in Alzheimer's in 2023 was brexpiprazole, which is an antipsychotic medication. And it wasn't because brexpiprazole was more effective than olanzapine or quetiapine. They weren't studied head-to-head. We don't know if it's more or less effective, but it was effective, just like those drugs were effective. And we don't really know if it has the same mortality risk or stroke risk because no one drug and no one study ever showed it. It was just pulling it together with all this data, but the company that developed brexpiprazole decided to study it in Alzheimer's disease with agitation, and they showed that the drug was safe and effective, and it was approved by the FDA.

And then, as you were just mentioning, the second drug for agitation in dementia was just approved this past spring. And the exciting thing with this medication, which

many of us haven't even used yet in clinical practice because it is new, is that it's not antipsychotic.

NANCY KEACH: And the name?

DR. BRENT FORESTER: The brand name is Auvelity. But it's a combination of two generic drugs that have been around for a very long time that we know a lot about. Those two medications are bupropion, which is otherwise known as Wellbutrin. It's an antidepressant. It's approved for depression. It's approved for smoking cessation. It's been on the market for decades, since the '80s and early '90s. So this medication is combined with another drug, which is called dextromethorphan. Dextromethorphan is the active ingredient in cough syrup. And the reason why the combination is used is because the Wellbutrin, bupropion, inhibits the breakdown of dextromethorphan. If you just took cough syrup, that dextromethorphan gets broken down into a metabolite, that's not good for your brain. But if you inhibit it with the bupropion, it stays as dextromethorphan, and it does some very interesting things in your brain to certain neurotransmitters that we think are responsible for treating agitation. It modulates the glutamate system and this thing called sigma 1 signaling.

So that combo was shown in clinical trials to reduce agitation in Alzheimer's disease without the risk in the worry of the mortality thing or the stroke risk, and it doesn't have the motor symptom side effects of the antipsychotics. What we don't really know is how it will work in clinical practice. My gut feeling, just knowing how it works and what I've seen in the research without having used it yet in these patients, is that it won't work as quickly because it's not inherently sedating, which on the one hand is a really good thing. We don't want to over sedate people. But we also know that the effect on agitation is not going to happen in a day or two. We're going to have to give it some time. So the relative severity of the agitation may dictate which medicine to use, in what situation.

NANCY KEACH: I want to ask some questions about Auvelity. Could you then take an antipsychotic, let's say for immediate sedation or immediate relief or some other drug and as you start Auvelity it might take about three weeks to start working? And I want to also point out, so it's not something that you would take on an as needed basis? It's something you take regularly, and the effect comes after about three weeks or so?

DR. BRENT FORESTER: First of all, any medicine that you give for agitation, you should give regularly, even if it's an antipsychotic. Using a medicine as needed for agitation is chasing something only when the symptoms occur, as opposed to preventing something from happening that could be problematic. You want it to go away and stay

away. You don't want to just treat it after it recurs. Really important point. Whether it's an antipsychotic or a drug like Auvelity that works very differently, I think the use of as needed only is not a good idea.

For antipsychotics like, say, olanzapine or brexpiprazole, if you figure out the dose that's helping but every once in a while there's a breakthrough symptom, then you can use a smaller version of that as needed to try to keep things calm in the moment if there's a breakthrough symptom. We do that all the time. And sometimes we do that when we're trying to figure out the right dose to get someone to is we'll put them on a certain dose during the day or at night. And then if they break through, we'll give them an extra as needed. And then we'll figure out over four to six weeks will they actually need a higher dose.

Auvelity is very different. Not only is the onset slower, but I don't think there will be any benefit in the next two or three hours in giving an as needed dose. It's just a very different kind of drug. So you wouldn't add an as needed. Then the last thing you said, which is really interesting, and it's theoretically possible that you could start an antipsychotic in an acute situation and after stabilization, after a month or two, gradually introduced the Auvelity as more of a maintenance treatment. No one's ever studied that, as far as I know. So that's theoretically interesting and I think clinically makes sense. But we haven't seen any data on that yet. So I don't know exactly how to comment.

NANCY KEACH: And you said it's a combination of two drugs, but you can't go get Wellbutrin and then get the other drug and take them. It's not the same thing as this drug, correct?

DR. BRENT FORESTER: It's not the same thing. And the dose is different. So it would be very hard to pair up from existing drugs, the combination that we're studied. And I wouldn't know what to say beyond what was studied in the trials.

NANCY KEACH: Got it. Colleen from Ottawa asked, "What are the safest drugs to use daily long-term for frequent, verbally aggressive agitation?" Is that an unanswerable question?

DR. BRENT FORESTER: Well, wouldn't it be nice if we had a different targeted medication for each one of these many symptoms we talked about? Well, so that doesn't occur. So when I think about verbal agitation that's frequent, I'll just say and empathize that may be one of the more challenging symptoms, because although physical agitation and depression and anxiety and paranoia often do respond really well, sometimes verbal agitation, I don't know why. I'm not sure if the data supports it,

but my own clinical experience is that's tricky.

I'll just reemphasize something we talked a lot about earlier, which is making sure we understand the cause of that verbal agitation, because that still is the key thing. But if we're going to choose a medication for a symptom like this that's common and recurrent, then I think it's really important that we find a medication that's going to be tolerable, that someone can take for a while. The antipsychotics generally are recommended for shorter term treatment because of side effect risks.

So medicines like the SSRIs. So the citalopram, which is an SSRI, serotonin reuptake inhibitor, this is a medication that was studied in a National Institute of Aging funded study called CitAD and Celexa is the brand name people are probably familiar with that. It's used for depression all the time, but that study demonstrated that a certain dose of Celexa, citalopram, is effective for agitation of all kinds, including verbal agitation. I think of the SSRIs as being first-line treatment for agitation like this. That's common, that's prevalent, that's causing distress, but is not an acute safety concern. The verbal agitation is going to upset more people around them than the person with the symptom. And so if you've got somebody who's physically aggressive and you need to calm them down now, citalopram is not going to do that. But if you've got verbal agitation or worry or pacing, things that are not imminently dangerous, an SSRI like citalopram is not a bad idea as a first-line treatment.

NANCY KEACH: Someone's wrote already 10 minutes ago. Please have him come back.

DR. BRENT FORESTER: Happy to!

NANCY KEACH: So yes, I have so many questions and so many medications and so many situations that people are asking about. So we talked about the antipsychotics. You have the Auvelity, I don't know what class that is. And then SSRIs, as the drugs that are available with the Auvelity most recently approved specifically for this condition, which is wonderful. Somebody wrote in, Ronald from Kirkwood, Missouri, "Is ECT still used for severe agitation?" And I mentioned this to you before and you said this is really interesting. So I'm bringing it up.

DR. BRENT FORESTER: All right. So I'll make a long story short, I love the question. I'm a geriatric psychiatrist and in my career, I've seen patients' lives saved by receiving ECT for major depressive disorder. Severe depression with paranoia and psychosis, and not eating and drinking and wanting to die. And they're a new person within weeks. And with periodic ECT thereafter and medication treatment and psychotherapy, their lives are just transformed. It's the most effective treatment we have for severe, recurrent, major depression. And it's indicated by the FDA for this.

About 20 years ago, while I was a medical director on an inpatient unit at McLean Hospital outside of Boston, we had a patient who came to us in her late 60s. She was 10 years into Alzheimer's disease, 10 years. She started developing symptoms of dementia in her late 50s. She was very early onset. She had profound agitation and aggression. She was assaulting her husband at home and on our inpatient unit. Everyone on the staff and the other patients, we tried a dozen plus medications. Nothing worked. And one of my colleagues said this question, what about ECT for severe agitation? And at the time, there was almost nothing in the literature. There were a few case reports that it might be helpful, and I thought it was-- not only why would this work, but cognitive side effects are the problem with ECT, and this person already has a mini mental status examination of near 0. And my colleague, very astute physician named Alex said to me, "Brent, what are our alternatives? We can't get her out of the hospital. No nursing home is going to take her and we can't keep her calm. And other than giving her narcotics to help her sleep and sedate her, I'm not sure what we could use."

So the family was on board, and she was medically cleared because she was otherwise very healthy 67-year-old. By the third treatment, she was smiling. By the eighth treatment, she went home and she stayed at home with her husband. And she went to her daughter's wedding about six months later. But she stayed home and received maintenance treatment once a month with us for the next 10 years. And then she died in her late 70s from metastatic colon cancer. I kept in close touch with her daughter, Karen, who's been very open about her mom's case. She's been on NPR, she's been in plenty of media talking about this. She talks about dementia and agitation. She worked for the Alzheimer's Association. She said, Brent, if you ever need help studying this, let me know.

So over the years, we started treating people like this woman and we saw similar effects. And one day, the Joint Commission came to survey our hospital and a nurse there said, a nurse surveyor said to my president at McLane, Bruce, your team is doing some interesting stuff with ECT in this population with dementia. You should study it. And Bruce said to me, my mentor said to me, Brent, you should study it. And so then we did. And that was 20 years ago. And so about two weeks ago, we finished our NIA funded trial. Five sites across the United States of people just like the patient I mentioned. It's not for mild agitation. It's not for people with easy to treat agitation that comes and goes. The people in our study failed three medications already. They had severe agitation on one of those rating scales I mentioned. And for the most part, their cognitive impairment was severe. They were receiving ECT, I would call this a palliative intervention.

In many ways, a lot of these treatments we talked about today, even the two that are

approved, are palliative interventions. They're used to improve quality of life. They don't extend life. They don't cure anything. They improve quality of life and symptoms, not just for the person with the illness, but for those around them, including their loved ones. That's the way we started thinking about using ECT. That's the way we designed our study and we're presenting our results, which are fascinating at the International Psychogeriatrics Meeting in Leiden in the Netherlands a week from today. So look for some information about the ECT study in dementia, which was included Alzheimer's type dementia, Lewy body dementia, vascular dementia and a condition we call frontotemporal dementia. I know that was a little long winded, but it's been a labor of love unfortunately, over 20 years. So it's very exciting.

NANCY KEACH: And it's encouraging. It's a positive-- and I'm already going to ask you to come back because I-- and to apologize to my audience because so many of you wrote in about what to do with a loved one who's being aggressive towards you and/or is it OK to walk away from that if they're being really cruel and all of these. And I'd really love to spend another hour specifically on those situations, because I really just wanted to get to the causes and the medications.

And so let me quickly ask two questions to wrap us up. I'm going to go a little over time, but Manmohan from Clive, Indiana asked, "Are there any pending medications that are nearer to approval or showing efficacy in phase III for agitation?" Is there anything else we should be looking for and watching for at this time?

DR. BRENT FORESTER: Yes, I do want to answer though, and address Nancy in a minute. But there are a number of trials going on right now in phase III for compounds that are trying to either for the psychosis of Alzheimer's or agitation in Alzheimer's, they're trying to get other indications. We're involved with two of those lumateperone, which is a medication that's on the market for psychiatric conditions, is being studied for these conditions, as well as a medication that's called KarXT, which is a same drug. It's just using a different name for medication approved for schizophrenia called Cobenfy.

So lumateperone is an antipsychotic but this other drug KarXT is actually a combination of a cholinergic agonist drug called xanomeline, which has been studied for decades for Alzheimer's disease to try to treat the cognitive and functional decline, but it caused too many side effects of nausea and vomiting, and other peripheral side effects. So it's combined with an anticholinergic drug that blocks the nausea and vomiting called trospium. So that's a combo drug, KarXT, lumateperone. Those are two that are in phase III. And there are others. Jeff Cummings, who's one of my colleagues and is one of the best known neuropsychiatric syndrome and dementia people in the world,

publishes a paper once a year where he goes through every sort of drug class that's being looked at for dementia, including behavioral symptoms of dementia. That's a great reference if anyone wants to look that up.

NANCY KEACH: We have had him on each of the three years that we're doing it. So he gives a report each year. But always good to remind everyone.

DR. BRENT FORESTER: Yeah, so there are others as well. But just so you know, now there's more activity in this area, which is wonderful. I would love to see a company really put resources behind studying cannabinoids, because I think there's a real opportunity for efficacy and safety there. And we just, again, I mentioned our work, but it's really early days there. Can I just say something about the really bad aggression and agitation?

NANCY KEACH: Of course.

DR. BRENT FORESTER: I just want to emphasize that the most important thing, if you have a loved one with agitation and aggression, number one is safety. Safety for you and for them. And sometimes to assure safety, we do things that are difficult. We may have to call the police. We may have to leave the situation. We may have to think about intervening with treatments that may sedate them for hours to a day, because we just need to get control. That does happen. And that's OK as long as we look for why. We still have to look for the why. Once the acute aggression is better and the situation is safe, then we still need to figure out, well, why did this happen? Because we can't let that happen again. And you should not feel like you're out on an island doing this on your own because you can't. I try to do that for both my dad, who just passed away, and my mom, who's now struggling because I'm an expert. So I figured, well, I know what to do, but I'm not their doctor. I'm their son. And I would just encourage all of you to make sure that you have the right clinical guidance for these situations because they're really, really hard.

Tom Harrison and I published a book a few years ago called *The Complete Family Guide to Dementia*, published by Guilford Press. I think it came out in 2022. Tom is a law journalist who had a mom with dementia, and I'm an expert in the field. And we wrote this book to really help you as a care partner throughout all phases of the illness, from diagnosis to end stage illness. And there's a big part of that book that talks about how to understand, how to manage, how to deal with, how to get help for these challenging behavioral symptoms like agitation. So I would encourage you to take a look at that. We had some resources in there as well as to where to turn for answers.

NANCY KEACH: I'm going to ask you one more question. Because it was your favorite

question and mine. And somebody else asked it again in the chat. So I'm going to read both of these people's question because I get this all the time. I've heard it answered badly. So I'm going to let you answer it wonderfully. Arthur in the chat wrote, "I once was told that an Alzheimer's patient's personality, agitation, aggression is a magnified reflection of how they were in earlier life. Is that true?" And the one I received in writing was from Mandy in Attleboro, Massachusetts, "Is there any correlation between the personality a person has always had and the personality changes they might have with Alzheimer's? For example, an unpleasant person is more likely to become more unpleasant than a person who has always been a delight to be married to?" So the way I've heard it asked in the past is when someone gets dementia and has neuropsychiatric symptoms, is this like exposing their true personality? And I'd love for you to answer that.

DR. BRENT FORESTER: Well, the way I would answer that wonderful question is the following. Number one, I don't think I've seen a study that's truly tried to answer that question. It would be very hard to do that study right.

NANCY KEACH: Spoken like a researcher. Thank you.

DR. BRENT FORESTER: So I'm thinking like a researcher there. Now, as a clinician, I would say that more often than not, there's no direct relationship. I have seen plenty of people who have told me that their mom was the most difficult, that they had the most challenging relationship, and they were so hard to be around. And now, in the setting of dementia, she's lovable, she's caring, she asks thoughtful questions. She's just a new person. And I've seen the opposite too, where people who are just salt of the Earth, amazing parents or spouses, unfortunately, are now experiencing these symptoms that we just described and they're hard to be around. That is not willful behavior that says anything about you as a person and as a care partner. That's the most important thing to remember.

This disease takes over someone's brain. And who we are comes from our brains. The biological substrate in our brain, ways that we really don't understand, whether it's chemical or structural, it's all there. So personality, behavior, mood, anxiety, all of those different constructs that we understand are changed by an illness that's causing a disruption in brain circuits, in brain cell function. It causes brain cell death, and it attacks different parts of the brain and different people at different times. And so one of the things that I often leave people with is, if you've seen one person with dementia, you've seen one person with dementia. Because this illness is different in everybody. And it may be that a preexisting personality will be happening, you'll see more of it when someone has dementia, but you also may not. So I don't think you can predict it,

unfortunately or fortunately.

NANCY KEACH: Thank you so much. Because for years, I worked with somebody who was considered a great expert and used to say, oh, yes, it's the person's true nature coming out, and I know that's not true. So thank you. Thank you for that. And thank you for staying a little over time. And I'm definitely having you back for another hour at least, because I apologize to everyone that I didn't get to so many of your questions. I'm really sorry for that. We will come back to this, I promise so that we can talk more clinically about how to deal with situations as they're happening.

So as our time today comes to a close, I want to thank first my wonderful colleagues at BrightFocus Foundation who've been trying to answer your questions in the chat and help produce this. Dr. Sharyn Rossi, our producers, Amanda Russell and Alexa Villarreal, my fabulous team, the team at MSquared who provides this technology platform. And especially thank you, Dr. Forester, for leaving the football game and sharing your expertise with us today. Really appreciate your time. You're amazingly articulate for a scientist, if I may say. You're able to talk in understandable language and we deeply appreciate that.

I just wanted to put up some helpline numbers for the newer drug, Auvelity, if you want to explore that as an option. They have a number 1-800-805-8621. You can call or a help group called Auvelity OnMySide at auvelity.com. And for Rexulti, the one that was previously approved 1-833-468-7852, rexulti.com.

I'm just going to say that we are going to be sending you a list of resources about agitation when we email you the recording of this episode. So you can look forward to that.

Last week, we launched our podcast, Let's Talk Alzheimer's. I'm happy to say, actually, it was two weeks. In the first two weeks, we have almost 80,000 views. Please go take a look at it. We're going to get this episode up on there as soon as we can. It's called Let's Talk Alzheimer's. Please go there, like, subscribe, and listen.

We have a lot of resources available at brightfocus.org including this infographic that shows all the drugs that are approved for Alzheimer's disease by the FDA. And we have a bunch of free publications for you that you can just call and ask for. Happy to send them out. Happy to provide all of this for free.

If this program would be helpful to someone you know, please share the link with friends. It's brightfocus.org/zoomin. We're over 7.5 million views for this program. So happy that that's the case. So if you know someone struggling with Alzheimer's, as we

all do, please share this link with them.

And finally, coming up on July 30, we have Dr. Jim Galvin talking about “Lewy Body, Alzheimer’s, and Mixed Dementias Explained.” Last month, we had vascular dementia. Next month, we’re going to talk about Lewy body and mixed dementias. So I hope you’ll all be there for that.

For those of you who’ve stuck with us, again, thank you so much for joining us for these episodes. This being the 44th. We really, really care. We really hope this was helpful to you. You can tell Dr. Forester cares tremendously. And so it’s our privilege to be able to try to translate the work that the researchers BrightFocus funds do and bring that information to you. This is our heartfelt, heartfelt mission at BrightFocus Foundation and clearly Dr. Forester’s heartfelt mission for his entire career.

And so I’m going to wrap up, as I always do, by saying that life is so short. Please tell the people that you love how much you love them. Give them a hug. Hold them close. Hi, mom. And tell them how much you love them. Keep them close to you. So thank you again. Thank you for coming. Please feel free to write in to us about other things you’d like to learn about. And have a great day. We’ll see you soon and be well. And, Dr. Forester, thank you so much. You can go off to the games now, off to the matches and really appreciate your time today. Thank you.

DR. BRENT FORESTER: Thanks, everybody. Really appreciate it.

Resources for Managing Agitation in Alzheimer’s

- FDA Approves Repurposed Anti-Depressant to Treat Alzheimer’s-Associated Agitation: <https://www.brightfocus.org/news/fda-approves-repurposed-anti-depressant-to-treat-alzheimers-associated-agitation/>
- Visiting With Relatives Who Have Alzheimer’s Disease: Some Tips for a Successful Visit: <https://www.brightfocus.org/resource/visiting-with-relatives-who-have-alzheimers-disease-some-tips-for-a-successful-visit/>
 - Includes communication tips
- Managing Negative Reactions: Minimizing the Triggers of Alzheimer’s Behaviors: <https://www.brightfocus.org/resource/managing-negative-reactions-minimizing-the-triggers-of-alzheimers-behaviors/>
- Challenging Behaviors in Alzheimer’s Disease: <https://www.brightfocus.org/resource/challenging-behaviors-in-alzheimers-disease/>

- Tips for Managing Sundowning: <https://www.brightfocus.org/resource/tips-for-managing-sundowning/>
- Alzheimer's Treatments:
 - Fact Sheet: <https://www.brightfocus.org/resource/treatments-alzheimers-disease/>
 - Infographic: <https://www.brightfocus.org/resource/fda-approved-alzheimers-therapies/>