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NPS Psychosis: Circuits, Treatment, and New Hope

Dr. Sabbagh:
This is CE on ReachMD, and I'm Dr. Marwan Noel Sabbagh. Joining me today is Dr. Dani Cabral.

Dani, can you tell us about neural circuits, and how they drive psychosis in Alzheimer's disease, and how do we use them to inform treatment?

Dr. Cabral:
Yeah, thank you for the question. And I just want to highlight, especially to the neurologists listening and watching, that we now know a lot more about the circuitry of psychosis in Alzheimer's disease, and this is really important that we are aware of this for our patients and families.

So in terms of, we have the symptoms of delusions and hallucinations that seem to arise when the Alzheimer's changes the pathology disrupt networks that are involved in salience attribution, emotional evaluation, reality monitoring, and sensory integration. And in practical terms, that points us toward a model involving fronto-limbic circuits, especially the amygdala and hippocampus, along with their connections through the thalamus and the basal ganglia and the frontal cortex. And so tau-related injury in these regions appears particularly relevant when it comes to these kinds of symptoms of psychosis.

Now clinically, I think of what's going on as the failure of the brain's ability to decide what's real, what's important, and what's emotionally safe. And we see this in our patients, right?

Now, in terms of that circuitry that's shaping the treatment, we have to remember that not all psychosis in a person with Alzheimer's is caused by Alzheimer's changes, right? So we need to always first look at all the potential causes, and those could be pain, anxiety, constipation, urinary retention, sleep disruption, medication effects, environmental overstimulation, boredom, all sorts of things.

And then also, we know about co-pathology, right? So we do think more of neuropsychiatric symptoms, and specifically visual hallucinations, when it comes to Lewy body disease, since some patients have both Alzheimer's and Lewy body disease, so we need to consider that could be involved.

Now, so when you have a patient presenting to you with psychosis, we always want to do nonpharmacologic approaches first. And so it's identifying those triggers that I just mentioned and reducing those, identifying unmet needs, and treating those firstly.

Now, if symptoms are severe, dangerous, or causing major distress, medication could be appropriate. And so there is still no broadly established Alzheimer's disease–specific approved treatment for psychosis itself, but studies are underway. And as we know, antipsychotics carry black box warnings specifically in individuals with Alzheimer's disease and related diseases, and so they can cause sedation, falls, cerebrovascular events, and increase mortality.

And so if medication is needed, practically speaking, what's often used in these severe situations would be an atypical antipsychotic. And again, these all have been off label until we now have the first approved treatment for agitation associated with Alzheimer's disease, which is brexpiprazole. So that's been a major advance to have a positive study in this area. Now that's for agitation, right? So that's what that was studied for, and not for psychosis. But this may be relevant, and these things are all interconnected, right? There's usually some kind of overlap or progression.

Now, probably the take-home to put this all together is psychosis in Alzheimer's disease, we know a lot more about the neurocircuitry involved, and we're learning more fronto-limbic and salience-related structures, and with growing evidence implicating specifically tau-related injury, because it's in those areas where those circuits are, like in the amygdala, hippocampal, thalamic, striatal pathways, and frontal regions. So that biology reminds us to treat psychosis as brain-based in Alzheimer's and not just a secondary manifestation or a reaction to external stressors. So I think that's what I want to share.

Dr. Sabbagh:
That's a lot, and thank you, Dani. It's amazing to me how we're starting to understand the pharmacological aspects, the neurotransmitter aspects, the neuroanatomical aspects, the feedback loops, and the disruption of the feedback loop in particular that are causing the emergence of the neuropsychiatric symptoms.

Our time is up, short and sweet and really gritty for practice. Thank you for listening.