Neurology, Cognition, Cognitive Screenings and Audiology, Part 2

By Douglas L. Beck, AuD, F-AAA, CCC-A

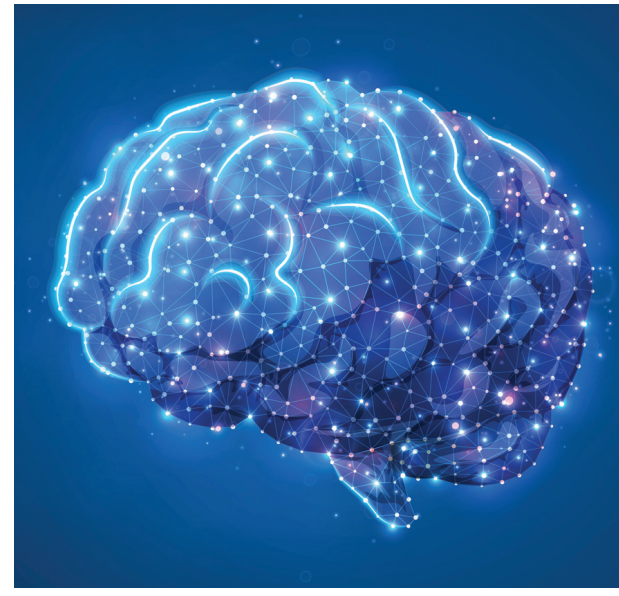
Welcome back to The Hearing Journal's *newest column, Perspectives With Dr. Beck. Dr. Beck's interview with James E. Galvin, MD, MPH, continues with an even deeper look into the nuanced relationship between audiology and cognition. Dr. Galvin is the Alexandria and Bernard Schoninger Endowed Chair in Memory Disorders and Professor of Neurology and Psychiatry & Behavioral Sciences at the University of Miami Miller School of Medicine. He is Founding Director of the Comprehensive Center for Brain Health, Director and Principal Investigator of the Lewy Body Dementia Research Center of Excellence, and Chief of the Division of Cognitive Neurology leading brain health and neurodegenerative disease research and clinical programs. If you missed Part 1 of this interview from the October issue of* The Hearing Journal*, catch up here: https://bit.ly/46Aps4L.*

Dr. Beck: Good morning, Jim. Thanks for joining me again to discuss pharmaceutical developments and realistic expectations for people with Alzheimer's Disease and Related Disorders (ADRD).

Dr. Galvin: I'm happy to help, Doug.

Dr. Beck: To review some of our previous discussion, we had discussed the *Lancet's* 2020 article[1], which indicated some 60% of dementia risk is due to age and DNA, and perhaps 40% is due to potentially modifiable risk factors, the largest of which was untreated hearing loss (8.2% PAF [population attributable factor]).

Dr. Galvin: Yes, and we discussed that some of the potentially modifiable risk factors interact with other listed and unlisted risk factors, too, and so it is not a simple fraction or percentage risk for any individual. Epidemiology provides us with very important trends and averages for a group, which does not necessarily tell us about the specific risks related to the individual we're assessing or treating. We really need to consider



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many different factors beyond those listed in the *Lancet* article, and all these things must be considered and weighted accordingly.

Dr. Beck: Agreed. Further, Nianago and colleagues (2022) reported the most significant potentially modifiable risk factor for dementia was mid-life obesity.[2] And so, all of this is evolving rapidly, and it seems we're left with nature versus nurture, or genetics and/or environmental factors as the primary risk factors. So, all that's old is new again!

Dr. Galvin: Yes, and so it's important to choose your parents carefully! But seriously, these potentially modifiable risk factors interact with each other, and they interact with your genetic makeup and all your lifestyle choices, factors, and habits. The result of these interactions varies from individual to individual. And so, all these factors are actually dynamically interrelated and focusing on just one factor may miss the forest for the trees. And so, if you're obese, you're more likely to have prediabetes and diabetes, and you may be insulin-resistant, and your blood pressure is more likely to be high. You may have hyperlipidemia and you're also at higher risk for cardiovascular and cerebrovascular disease….and so, obesity interacts and cascades with other things, as does hearing loss, untreated high blood pressure, and more. We have to be very careful when we address or focus on just one factor. That said, nothing happens at all if we don't look for, suspect problems, and screen appropriate candidates to decide if there is a normative or a

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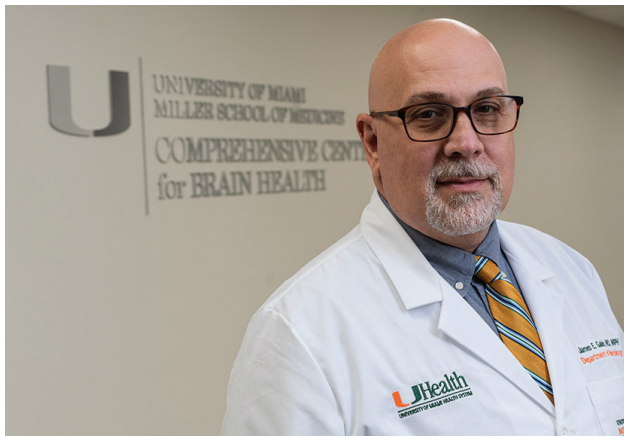

James E. Galvin, MD, MPH

non-normative result, and then we have to act on those screening results.

Dr. Beck: That makes sense. If we're going to screen someone for cognitive or other problems, we have to be prepared to refer patients with non-normative results. Let's spend a few moments discussing where we are with pharmaceuticals. It was only about two years ago that the FDA approved the first drug (aducanumab) to slow down the progression of Alzheimer's, and as I recall it was quite a controversial decision.

Dr. Galvin: It was a somewhat controversial decision at that time based on the trial data that was available. This was one of the first, if not the first, neuroscience drugs to receive accelerated approval from the FDA, which also added to some of the debate. Although there has not been much clinical use of aducanumab (Aduhelm®), the approval did help make a pathway for approval of other anti-amyloid medications. Lecanemab (Leqembi®) received accelerated approval in January 2023 and full approval in July 2023. This was followed by an important decision by CMS to provide coverage of these medications with the condition that the physician be part of a national registry. It is important to remember that these medications are *not cures* but instead represent the first disease-modifying therapies specifically to target buildup of beta-amyloid plaques in the brain. These results were published in the *New England Journal of Medicine* in 2022.[3] Although the benefits were statistically significant, the overall clinical effect is modest, and it is important to note that these drugs have potential side effects as well.

Another member of this family of monoclonal antibodies, donanemab, has also completed its Phase III trial. These results were published in the *Journal of the American Medical Association* in 2023.[4] Both the lecanemab and donanemab studies support that the diagnosis and treatment of Alzheimer's disease in the earliest stages is more likely to produce clinically significant results. A major difference between the lecanemab and donanemab studies was that donanemab appeared to demonstrate greater clearance of amyloid plaque, with a mean clearance of 84% at 18 months, compared with a 1% decrease for participants on placebo.

Dr. Beck: All of which is quite remarkable. Progress is happening at an amazing speed.

Dr. Galvin: Absolutely. And every single outcome in both the lecanemab and donanemab trials were markedly different between the placebo and the treated groups. Also, it's important to note that as more amyloid plaques are removed through pharmaceuticals, the side effects potentially increase, too. There appears to be a "sweet spot" where we need to remove enough amyloid to get a good clinical effect, but we have to balance that with side effects, which include brain swelling, cerebral hemorrhaging, and others.

Dr. Beck: Can one draw a conclusion about amyloid and cognition?

Dr. Galvin: No. There is no correlation between amyloid and cognition. Amyloid is necessary but not sufficient to cause Alzheimer's disease. To have clinical Alzheimer's disease, amyloid must be present, but other things have to also occur such as tau tangles, inflammation, neuronal injury, neuronal loss, and more. So, when you have a combination of these things present, you often have the clinical manifestation of Alzheimer's disease, which generally starts with MCI and then becomes Alzheimer's disease dementia. But there are people with all these biological markers, who are clinically normal, and they might be characterized as having preclinical Alzheimer's disease. This is changing how we think about disease and how we will need to diagnose it in the future. You will need both the clinical manifestations and the presence of biomarkers of Alzheimer pathology in order to make the diagnosis and offer patients these disease modifying medications. This is just an example of how the principles of precision medicine are now being applied to Alzheimer's disease and other brain disorders.

Dr. Beck: Thanks, Jim. I certainly appreciate your insight and knowledge on these very important issues. Seems to me that with the rapid progression of successful pharmaceuticals, we'll see an ever-increasing number of treatments in the near future.

Dr. Galvin: Yes, I think the future is bright for screenings, diagnostics, and treatment of Alzheimer's disease patients, and I expect continued advances and improvements over the upcoming years.

Dr. Beck: Thanks, Jim. This has been a fascinating discussion and I am very appreciative of your time, knowledge, and expertise.

Dr. Galvin: Thanks, Doug. I appreciate the opportunity to address the hearing care professionals and I want to be clear that cognitive screenings are step one in addressing these issues. And just like all other areas of medicine, the best outcomes occur with early identification and treatment.

References for this article can be found at http://bit.ly/HJcurrent.