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Democracy Dies in Darkness

Sound waves get Alzheimer's drug past brain barrier, small study shows

By Mark Johnson

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In the first study of its kind in humans, researchers have discovered that it is safe to use sound waves fired into specific areas of the brain to open a protective barrier and clear the way for Alzheimer's medications. The study, reported in the New England Journal of Medicine, involved just three patients, but it raises hope about the long-term potential of the treatment strategy known as focused ultrasound.

"We want to be very cautious. This is the first three people in the world that have had this [treatment]. What we've learned from this, I think, can help us," said Ali Rezai, lead author of the study and executive chair and director of the Rockefeller Neuroscience Institute at West Virginia University.

Rezai stressed that the goal of the research is not to replace pharmaceutical treatments but to improve their benefits by helping more of the drug penetrate the brain.

Nature has provided humans with a barrier made of tightly packed cells that blocks harmful toxins, such as viruses, bacteria and fungi, from reaching the brain. Known as the blood-brain barrier, this shield has for decades presented a major challenge to scientists trying to treat neurodegenerative diseases such as Alzheimer's and Parkinson's, which afflict at least 7 million Americans. The barrier is a locked door that stops about 98 percent of treatments from reaching the brain.

With focused ultrasound, Rezai explained, "what we want to do is push individuals toward the milder stages of Alzheimer's with less plaques to give them a fighting chance."

Two men and a woman suffering from mild loss of memory, learning, concentration and decision-making skills due to Alzheimer's took part in the study. The patients, who ranged in age from 59 to 77, were given six monthly doses of the federally approved — if somewhat controversial — lab-made antibody aducanumab, sold under the brand name Aduhelm. The antibody, which is administered directly into a patient's vein, reduces a sticky substance in the brain called amyloid beta, which clumps between neurons and disrupts their function.

About two hours after giving patients the medication, researchers used focused ultrasound to open the protective barrier in one hemisphere of a patient's brain, but not in the other. The hemisphere that received focused ultrasound plus the antibody saw harmful amyloid beta plaques reduced by an average of 32 percent more than the other brain hemisphere.

Using bubbles to access the brain

Focused ultrasound was first approved in 2012 to relieve pain caused by cancer that has spread to the bones.

The technology, now in various stages of development and testing for numerous medical conditions, involves delivering tiny microbubbles to a patient's body through an intravenous line. The patient wears a special helmet that allows sound waves to be fired through their skull to precise locations in the brain; the locations are identified using MRI machines. The sound waves to these precise points cause the microbubbles to expand and contract, temporarily opening the blood-brain barrier.

The technique has been used to help cancer treatments reach tumors inside the brain, but its application is more complex with Alzheimer's patients, whose brains tend to be more fragile, Rezai said.

"I think it's a very exciting pilot study that opens the door for more extensive investigation on the potential of focused ultrasound" for getting lab-made antibodies and other drugs into the brain, said Eliezer Masliah, director of the division of neuroscience at the National Institute on Aging, part of the National Institutes of Health.

Masliah said scientists have also been exploring a second technique for getting medicines past the blood-brain-barrier, known as the "Trojan Horse" approach. The technique is named after the large wooden horse in mythology said to have been mistaken as a gift by the Trojans, who took the horse inside their gates — along with the Greek warriors hidden in its belly.

In a pharmaceutical Trojan Horse, researchers link a drug to another molecule that recognizes a receptor in the blood-brain barrier. This receptor helps the drug cross the barrier and reach the brain. Another strategy called transcytosis works like a relay race, in which molecules hand off the drug to one another as if it were a baton.

The new study does not represent the first time that focused ultrasound has been used on patients with Alzheimer's. Alzheimer's patients took part in a 2018 study, though they were given antibodies to treat cancer that had spread to the brain, not Alzheimer's.

Previous studies that used focused ultrasound without any Alzheimer's medication have suggested that the sound waves by themselves may provide a small benefit to patients. Rezai said the process activates the lymphatic system, which directs the brain's immune response.

Joshua Grill, professor of psychiatry and human behavior at University of California at Irvine, called the study "biologically very exciting," adding that the research may help scientists understand why some Alzheimer's drugs work better than others. Scientists want to understand, for example, whether the important factor is how low you can get the amyloid levels, or how fast you clear them away.

Grill also sounded a note of caution, saying that while focused ultrasound may increase the effectiveness of the antibody treatment by allowing more of it to reach the brain, it may also significantly raise the intensity of side effects. In the case of aducanumab, side effects can include seizures, nausea, confusion and headaches.

"We have the blood-brain barrier for really important reasons to protect our most important organ," Grill said.

He stressed that years of work will probably be needed before focused ultrasound treatment can become an approved option for patients: "We're nowhere near that now."