Two new Alzheimer's drugs show promise in early studies

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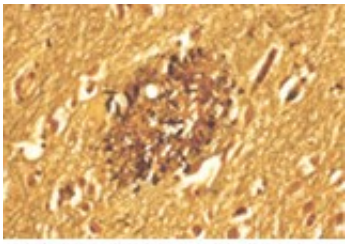

Alzheimer's disease plaque. Photo: U.S. National Institute on Aging

Experts caution that expectations are low in field littered with drug failures.

(HealthDay)—Researchers say two new drugs for Alzheimer's disease have shown promise in early experiments and will likely progress to the next round of clinical trials.

One drug, called a BACE inhibitor, has been in development for more than 10 years. In very early tests, it dramatically reduced levels of beta amyloid, a sticky protein that forms plaques in the brains of Alzheimer's patients.

The second drug is thought to reduce damaging inflammation. Patients with mild mental impairment who took the drug for over a year saw significant improvements in some measures of memory and thinking.

The results of the studies, both sponsored by companies hoping to market the medications, are scheduled to be presented Sunday at the Alzheimer's Association International Conference, in Boston.

Normally, those reports would be cause for optimism in a disease that affects 5 million people and currently has no effective treatments.

But Alzheimer's experts have been through this dance before, and they say they're not holding their breaths that the new drugs will make it to patients.

"It's like that movie '27 Dresses,'" said Dr. Paul Rosenberg, an associate professor of psychiatry and behavioral sciences at Johns Hopkins University School of Medicine, in Baltimore. "We've been bridesmaids in this field so many times."

So far, the search for a drug that might slow or stop the relentless march of Alzheimer's disease through the brain has proved fruitless.

In the past year alone, three closely watched new agents failed in late-stage clinical trials. In May, a Massachusetts pharmaceutical company announced it would close after its experimental Alzheimer's drug ran into unexpected safety problems. In June, Eli Lilly stopped a study of a different BACE inhibitor when patients who were taking the drug showed signs of liver problems.

Those disappointments come on top of years of trying—and failing—at other promising approaches. The plaques that clog the brains of Alzheimer's patients seem to be accelerated by high cholesterol in the blood. So researchers tried cholesterol-lowering drugs in Alzheimer's patients. That didn't work. Doctors noticed that the brains of people with Alzheimer's are very inflamed, so researchers mounted large trials to test over-the-counter anti-inflammatory medications against memory loss.

They were of no help.

Indeed, most drugs in development face long odds of success. Only about 8 percent of drugs that reach human trials will eventually make it to market, according to the U.S. Food and Drug Administration.

"In the Alzheimer's field, it can be said to be zero, because we haven't a new drug in 10 years," said Rosenberg, who was not involved in the studies.

Hard as it is to hold out hope, Rosenberg said he probably would attend the presentation of the latest trials because, as he put it, "This is way new stuff."

The first study tested a drug called CHF5074 that's made by an Italian company called Chiesi Pharmaceuticals. The drug is believed to turn down inflammation in the brain by modulating microglial cells.

Microglia are the housekeepers of the brain. They keep its connections free of unwanted garbage, but they also produce chemicals that trigger inflammation, which can become toxic over time.

Ninety-six patients took one of three different doses of the drug or a placebo for the first 14 weeks of the study. Then researchers opened the trial, allowing study participants who wanted to continue to keep taking their original drug dosage. Seventy-four people chose to remain on the drug. All the patients had mild cognitive impairment, an early stage of memory loss that sometimes progresses to Alzheimer's disease.

Fourteen patients dropped out of the trial early. Three left because of adverse events. The main side effect reported in the study was diarrhea, which affected 16 percent of patients on the highest dose of the drug.

After 16 months on the drug, patients who remained on the drug saw significant improvements on some tests of memory and problem solving. The drug appeared to work especially well in patients who carried a gene called APOE4, which confers the highest genetic risk for Alzheimer's. APOE4 carriers saw improvements in test scores that were about one-third to one-fourth higher than before they started the study.

"Our study shows that we may, may, in some way help patients with their memory, perhaps because we're keeping the microglia from overactivity," said study leader Dr. Joel Ross, president of the Memory Enhancement Centers of America in Eatontown, N.J.

Experts who were not involved in the research saw reasons for caution with the results.

"With [74] patients, you can't jump up and down about some symptoms improving in some patients," said Greg Cole, associate director of the Alzheimer's Center at the University of California, Los Angeles. "It's also not clear what the nature of the microglia modulation is exactly."

Study authors admit they don't know exactly how the drug works, either. But they said they're already planning larger studies to try to confirm their finding.

The second drug being presented at the meeting, a BACE inhibitor that's being developed by Merck, has the opposite problem. Researchers know exactly how it does what it does. They don't yet know whether it will help patients.

BACE inhibitors block an enzyme that cleaves a large protein in the brain into smaller pieces of sticky beta amyloid, a substance that forms telltale plaques in the brains of Alzheimer's patients. Blocking the enzyme blocks production of beta amyloid.

"It's been an important target. It took the drug companies at least a decade to develop this class of drugs," Rosenberg said. "Drug companies did a lot of black magic to get this drug into the brain. It's really compelling that this drug really does what it says it does."

In this study, which was mainly designed to check the safety of the drug, researchers assigned 30 patients to take one of three drug dosages or a placebo for seven days. Patients on the highest doses of the drug saw reductions in beta amyloid in their spinal fluid of over 80 percent. Researchers say they saw no evidence of adverse effects.

"We can reduce amyloid to unprecedented levels," said Dr. Mark Forman, a senior principal scientist at Merck, the company that's developing the drug.

The problem, skeptics say, is that medications have been used to reduce beta amyloid before, and those had no clinically meaningful benefits for patients, at least for those already diagnosed with the disease. There have been some signs that lowering beta amyloid may be helpful for people who haven't yet begun to show symptoms of memory loss.

Forman said he thinks BACE inhibitors have a better chance of working, however.

"BACE inhibitors blocks the generation of amyloid at the very first step in its production. It's very different from what some of the other studies have done with antibodies that are really promoting the clearance of beta amyloid after it's formed," he said.

Experts agreed that the drug seems to work well to lower beta amyloid.

But, "It remains to be seen when you can do that and for how long and achieve a useful, clinical benefit," Cole said. "That's what we don't know

and it will be a long time before we can figure that out."

Research presented at medical meetings should be viewed as preliminary until published in a peer-reviewed journal.

More information: To learn about medications available to treat Alzheimer's symptoms, head to the Alzheimer's Association.