

# Trying to solve the Alzheimer's puzzle

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Despite a 99 percent failure rate and another major setback recently, Alzheimer's researchers are plowing ahead with hundreds of experiments - and a boost in federal money - to try to crack a deadly disease that has flummoxed them for decades.

A law passed by Congress in December and signed by former President Barack Obama sets aside \$3 billion over 10 years to fund research of brain diseases and precision medicine, a shot in the arm for Alzheimer's research. The law, called the 21st Century Cures Act, also includes prize money to encourage Alzheimer's experiments.

But billions of dollars have so far made little progress in decoding the memory-robbing disease, which affects 5 million Americans. Alzheimer's is currently the nation's sixth-leading cause of death. Decades of research have not produced a single drug that alters the disease's course.

December began with another major setback: Eli Lilly shared disappointing results of a late-stage clinical trial of its experimental drug solanezumab, which failed to significantly slow Alzheimer's progression.

But scientists aren't giving up on the main hypothesis behind Eli Lilly's trial: that Alzheimer's can be defeated by using drugs to attack amyloid "plaques" that build up in the brain of Alzheimer's patients. Some scientists believe these cause the disease.

Many observers still hold out hope for another promising anti-amyloid drug, Biogen's aducanumab, which in an early trial improved cognitive decline in a small number of patients.

Other potentially groundbreaking research aims to intervene before patients even feel any symptoms. Using PET scans, scientists can now identify amyloid plaques building up in a patient's brain years before they develop Alzheimer's. The A4 study, for instance, is testing solanezumab in adults who are accumulating amyloid plaques, but showing no outward signs of Alzheimer's, such as memory loss or cognitive decline.

Other scientists are targeting what they believe is the true culprit, the protein tau, which creates "tangles" in the brain, the disease's other primary marker.

The experiments continue against a bleak backdrop: No new Alzheimer's therapies have won federal approval since 2003, and Alzheimer's clinical trials have had a 99 percent failure rate. Patients can access only four Food and Drug Administration-approved Alzheimer's drugs that alleviate symptoms but do not prevent, slow or reverse brain damage.

"The history of clinical trials results has been a history of disappointment," said Keith Fargo, director of scientific programs and outreach at the Alzheimer's Association.

Still, 77 Alzheimer's drugs are currently being investigated or developed, according to the trade group PhRMA. And other experiments seek to repurpose FDA-approved drugs for other conditions, such as diabetes or cancer, to see if they can help Alzheimer's patients - and cut several years from the drug development process.

Non-pharmaceutical solutions are also being explored. Observational studies have shown that people who exercise more and have healthier diets seem to get the disease later in life. Researchers are now conducting trials to more closely measure the effects of exercise and diet. One randomized trial underway at Wake Forest University, dubbed EXERT, is testing the effects of high-intensity aerobic exercise on adults with mild cognitive impairment by enrolling them in exercise programs at a YMCA.

Even before December's passage of the 21st Century Cures Act, public funding for Alzheimer's research has been rising. The National Institutes of Health allocated almost \$1 billion to Alzheimer's research in fiscal 2016 - a \$350 million increase over the previous year, according to

Laurie Ryan, chief of NIH's Dementias of Aging Branch. There are 468 open [clinical trials](#) related to Alzheimer's, and over a hundred more in progress, listed on the government database ClinicalTrials.gov.

Meanwhile, Alzheimer's advocates still grapple with a basic question: Is the rate of Alzheimer's actually going down? A study in JAMA in November found that even as scientists have made no progress in changing Alzheimer's course, overall dementia rates, which include Alzheimer's and other dementias, appear to be dramatically declining. The paper cast doubt over a major talking point of the Alzheimer's lobby: That as baby boomers age, the number of Americans living with Alzheimer's will explode from the current 5 million to 14 million in 2050. The study also suggested that lifestyle changes may make a difference.

While some heralded that as good news, others downplayed the finding.

Even if dementia rates drop, Alzheimer's remains a major killer, and the number of afflicted people will likely still rise, because the U.S. population is aging so rapidly, predicted Fargo. He also questioned the study's methods, which relied largely on telephone interviews.

"It's not time to let our foot up off the gas," Fargo said.

Eli Lilly's closely watched trial, dubbed Expedition 3, was the latest potential breakthrough to fall flat. In 2,100 people with mild dementia, solanezumab failed to show significant results compared to a placebo.

Some critics said the failure casts doubt on the hotly disputed hypothesis that Alzheimer's is triggered by the buildup of amyloid plaques.

But Eli Lilly spokeswoman Nicole Hebert said more work is needed to test the hypothesis, because the trial explored just one method of

removing amyloid, on one subgroup of people. She said the company is pursuing seven other lines of attack.

"Rumors of the death of the [amyloid hypothesis](#) have been around for many years, and they're probably premature," Fargo agreed.

Fargo noted that brain imaging has shown that [amyloid plaques](#) start to build up 15 to 20 years before signs of dementia appear. So to really test the amyloid hypothesis, he said, scientists may have to intervene earlier than they did in Expedition 3.

Despite the latest failure, Fargo said, "there's still more optimism in Alzheimer's research right now than there has been for 10 years."

The answer to Alzheimer's, Ryan said, is not going to be one "magic bullet," but an array of solutions tailored to different patients.

Will scientists ever find a cure?

Dr. Ron Petersen, director of the Alzheimer's Disease Research Center at the Mayo Clinic, isn't betting on it. But there's still "a lot going on to be hopeful about," he said.

"I think slowing the progression and/or delaying the onset, are realistic goals."

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