Vox

A promising drug to slow the progression of Alzheimer's was just unveiled

"It's a cautious hope."

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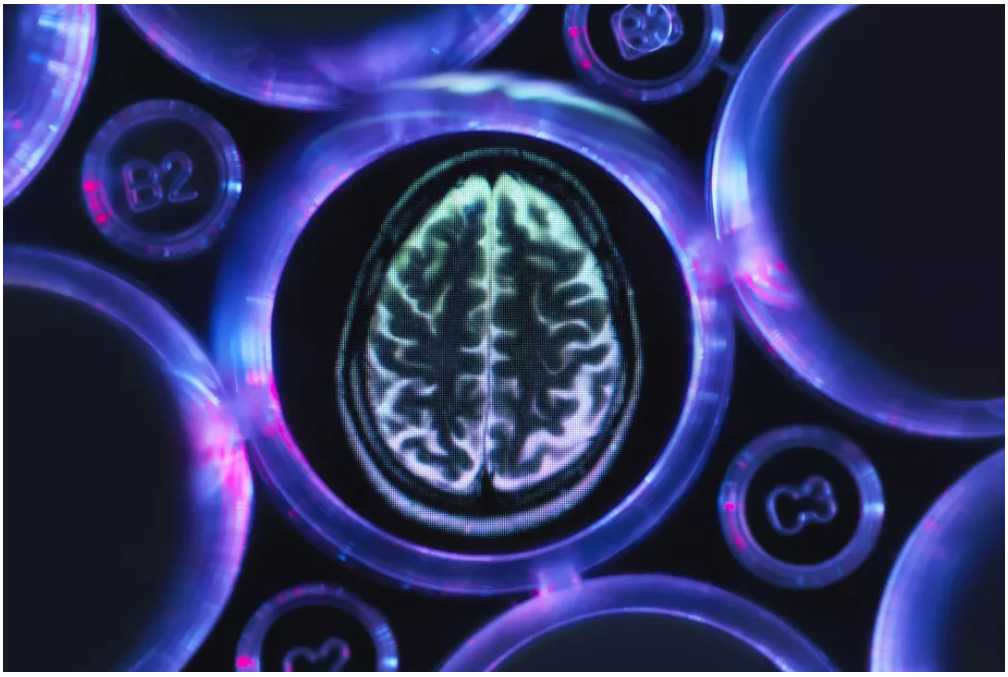

Despite the fact that Alzheimer's is the most common cause of dementia in older people, there is not a single drug available to treat the condition. | Getty Images/Cultura RF

Alzheimer's is one of the deadliest, **costliest, and most emotionally draining diseases in this country**. Yet we have no drugs to reverse the condition, and the last medicine that came on the market to treat Alzheimer's symptoms was approved some **15 years ago**.

So it's no surprise that Alzheimer's researchers, patients, and **investors** were eagerly anticipating the results of a phase 2 study on a potentially promising new medication, called BAN2401, from the drugmakers Biogen and Eisai.

On July 5, **the companies released a summary of the findings** from a trial of the drug involving 856 patients with early Alzheimer's, showing the medication could slow the progression of the brain-ravaging illness. On Wednesday afternoon, they **presented** more details about their findings at the **Alzheimer's Association International Conference** in Chicago.

The results have sparked cautious optimism. “Millions of people have Alzheimer’s, and right now it’s a death sentence. So any time we see positive results from a trial that appears to show disease modification, that gives us hope,” said Keith Fargo, director of scientific programs at the Alzheimer’s Association. “But it’s a cautious hope.”

That’s because, while the experimental drug is potentially exciting, and may represent a step forward in the grinding, frustrating quest to treat Alzheimer’s, it’s far from being ready to prescribe to patients.

First, the results haven’t been peer-reviewed, much less replicated by other researchers. Also, the way the drug companies ran and analyzed the data in their trial makes some experts suspicious. That’s why, with a huge market for an effective drug and massive potential profits at stake, we need to evaluate the new drug very, very carefully.

The drug slowed Alzheimer’s progression by 30 percent, according to the drug company

Before we explore why there’s reason to question the early results, let’s briefly touch on why they may potentially be significant.

First off, Alzheimer’s is an extremely complex disease of the brain. It’s not caused by a single cell failure. Instead, the best scientific understanding of what’s likely going on with Alzheimer’s is called the “amyloid hypothesis.” Beta-amyloid is a protein in the brain, and when it’s metabolized abnormally, it sets off a cascade of events that eventually kills the nerve cells in the brain and causes the brain to shrink. Years (or even decades) after this process begins, people start to experience the hallmark symptoms of Alzheimer’s, like forgetfulness and confusion.

Despite the fact that **Alzheimer’s is the most common cause of dementia** in older people — and there are an estimated 5.7 million Americans living with the disease — there is not a single drug available to treat the condition. (The medications on offer only ameliorate Alzheimer’s symptoms — like **anxiety, aggression, and depression** — and only in some people.)

The path to finding a drug that would stop the progression of or reverse the disease **has been littered with failures**. And that’s largely because of how complicated Alzheimer’s is.

“It’s a complex system failure — multiple areas of the brain that depend on each other fail,” said Ronald Petersen, director of the Mayo Clinic Alzheimer’s Disease Research Center. So despite spending billions of dollars on research into a variety of therapeutic

approaches, there have been no new drugs in 15 years. And while amyloid buildup is necessary to diagnose the disease, there are many potential contributors to Alzheimer's — including genetics or a history of head injury or stroke.

The new, experimental medicine, BAN2401, purports to test the aforementioned amyloid hypothesis. When amyloid protein is misprocessed, it begins to accumulate in the brain, forming a sticky buildup outside the nerve cells called beta-amyloid plaques. The accumulation of amyloid also stimulates an immune response, which causes another set of proteins (the tau proteins) to form tangles inside the nerve cells. BAN2401, which is delivered intravenously, is an antibody that helps the immune system fight that disease process.

"The theory is if we can interrupt the plaque formation, and these toxic forms of amyloid, hopefully we can interrupt that whole process and slow down memory loss — and that's why we're excited about this finding," said Stephen Salloway, the director of neurology and the memory and aging program at Butler Hospital in Providence, Rhode Island, and a professor of neurology at Brown University. (He wasn't involved in the trial but also runs clinical trials for Biogen.)

In the **placebo-controlled, double-blind, randomized study** of 856 patients with early Alzheimer's, the drug companies said brain scans showed that higher doses of the medication were able to reduce amyloid plaques after 18 months. They also used an Alzheimer's scale (called **ADCOMS**) to measure clinical symptoms in the patients, and found that the reduction in plaques corresponded with a slowing of **Alzheimer's disease progression by 30 percent**. The most common side effect was allergic reaction at the site of infusion, and some patients experienced brain swelling.

"We think this result is really the first of its kind," Lynn Kramer, chief medical officer of Eisai's neurology business group, said in a **press briefing Wednesday**, and "robust enough to approach regulatory authorities to discuss next steps."

If the results are indeed solid, and the drug is approved for market, it could mean people with early-stage Alzheimer's might be able to keep the disease at bay. It could also mean that we finally have an actual treatment for the disease, and not just its symptoms, available for patients.

The drug still needs to pass a phase 3 clinical study and FDA scrutiny

But again, there's reason to be cautious with these findings. Today's data, unfortunately, can't definitively answer the question of whether this is truly an Alzheimer's breakthrough.

First, the trial was a phase 2 study, and the drug will likely need to pass a phase 3 trial, involving a larger group of people to confirm its effectiveness and monitor any side effects before it can be approved by the Food and Drug Administration. "We want to make sure the data are meaningful and reproducible, and I think doing another trial to be able to reproduce the results would make good sense," Salloway said.

The results are still preliminary and not yet peer-reviewed or published. While it's not unusual for drug companies to release their data at conferences ahead of publication, it means they haven't yet been externally scrutinized.

The researchers also used a **complicated study design** that will need to be vetted. The trial was initially designed to test people's responses to five dosage levels of BAN2401, compared to placebo, for one year, using an "adaptive" approach, meaning they could shift people from one dose group to another depending on how they were responding to the drug. They then used Bayesian statistics to analyze their results, and found the medication didn't work after running the trial for 12 months. They **released those failed results in December 2017**.

But when they used more traditional statistical methods to reanalyze their data, and ran the trial out to 18 months, voilà — the drug appeared to work at the highest doses.

Now, it's possible we'll learn that dubious data crunching was used to make the drug look more favorable after an initial flop. (While changing a **trial's endpoints midway through is bad science**, a spokesperson at Biogen said the 18-month endpoints "were all pre-specified.")

"We have to be cautious not to overinterpret or overinvest in a study like this until we see it [published and peer-reviewed], and maybe it needs to be replicated, or maybe it needs to be expanded," said Petersen, who has consulted for Biogen but was not involved with this drug or this trial.

Either way, today's news is more like the potential beginning of the journey to an Alzheimer's breakthrough — and, unfortunately, not an end.