A Dangerous Silver Bullet

Drugs that hit an Alzheimer's target are gaining traction. Some neurologists remain dubious

By Liz Seegert

ONE OF NEUROLOGIST Anelyssa D'Abreu's least favorite tasks is giving her patients a dreaded diagnosis: early-stage Alzheimer's disease. But it's not quite as bad as it used to be. Today when they ask, "Is there anything we can do?" D'Abreu has a new answer: "Perhaps."

Unlike a decade ago, when D'Abreu had little to offer her patients with Alzheimer's, there are now drugs that may impede the disease's progression. The difficulty with this approach, however, is that it comes with a trade-off. The new medications carry the risk of serious side effects, including brain bleeds, stroke-like symptoms and even death. Yet they also come with hope, something new for Alzheimer's patients and their families.

Drugs in this class, known as anti-amyloid therapies, have not gained much traction. In limited studies, they have been shown to slow or even decrease one of the biological symptoms of Alzheimer's: the accumulation of amyloid beta in the brain. Nearly four dozen studies on these drugs have been conducted since 2018, and collectively they indicate that anti-amyloid therapies may marginally reduce the rate of cognitive decline. Some experts say that could offer perhaps an additional year of independence. But the clinical trials completed to date rely on only 18 months' worth of published data, and their success has been tempered by the drugs' significant downsides. Additionally, the framing of these drugs' success has come under criticism.

D'Abreu, who heads the University of Virginia neurology department's cognitive and behavioral neurology division, was initially apprehensive about offering antiamyloid treatments to her patients with early-stage Alzheimer's. A relatively high percentage of participants in the anti-amyloid studies experienced brain swelling and microbleeds, events known as amyloid-related imaging abnormalities (ARIA), which can lead to disability or even death. Up to 40 percent showed brain swelling, and up to 28 percent had brain bleeds. D'Abreu wasn't the only physician who hesitated over such potentially severe side effects.

In general, researchers and clinicians were highly skeptical of these drugs when they were introduced. They had shown promise in clinical studies but are only now yielding enough data in real-world scenarios for scientists to gain a better understanding of their efficacy. After much thought, D'Abreu decided it was important to offer her patients the option. When people are functionally independent, she says, delaying progression toward full-blown Alzheimer's is a big deal. "If it really slows down a person in the mild-cognitive-impairment stage, that makes a huge difference," she says. Among the 50 or so people at her hospital who have received the therapy so far, none have experienced any serious adverse effects.

Alzheimer's affects about 7.2 million people over age 65 in the U.S., according to the Alzheimer's Association, and about 74 percent of them are 75 or older. Scientists have been seeking treatments for decades; because amyloid beta plaques can begin accumulating long before noticeable symptoms appear, most efforts aimed to clear them from the brain and prevent the formation of new ones. In 2021, when the U.S. Food and Drug Administration fast-tracked the first anti-amyloid therapy, some hoped it would be what patients and providers had been waiting for: a drug that could stop Alzheimer's in its tracks.

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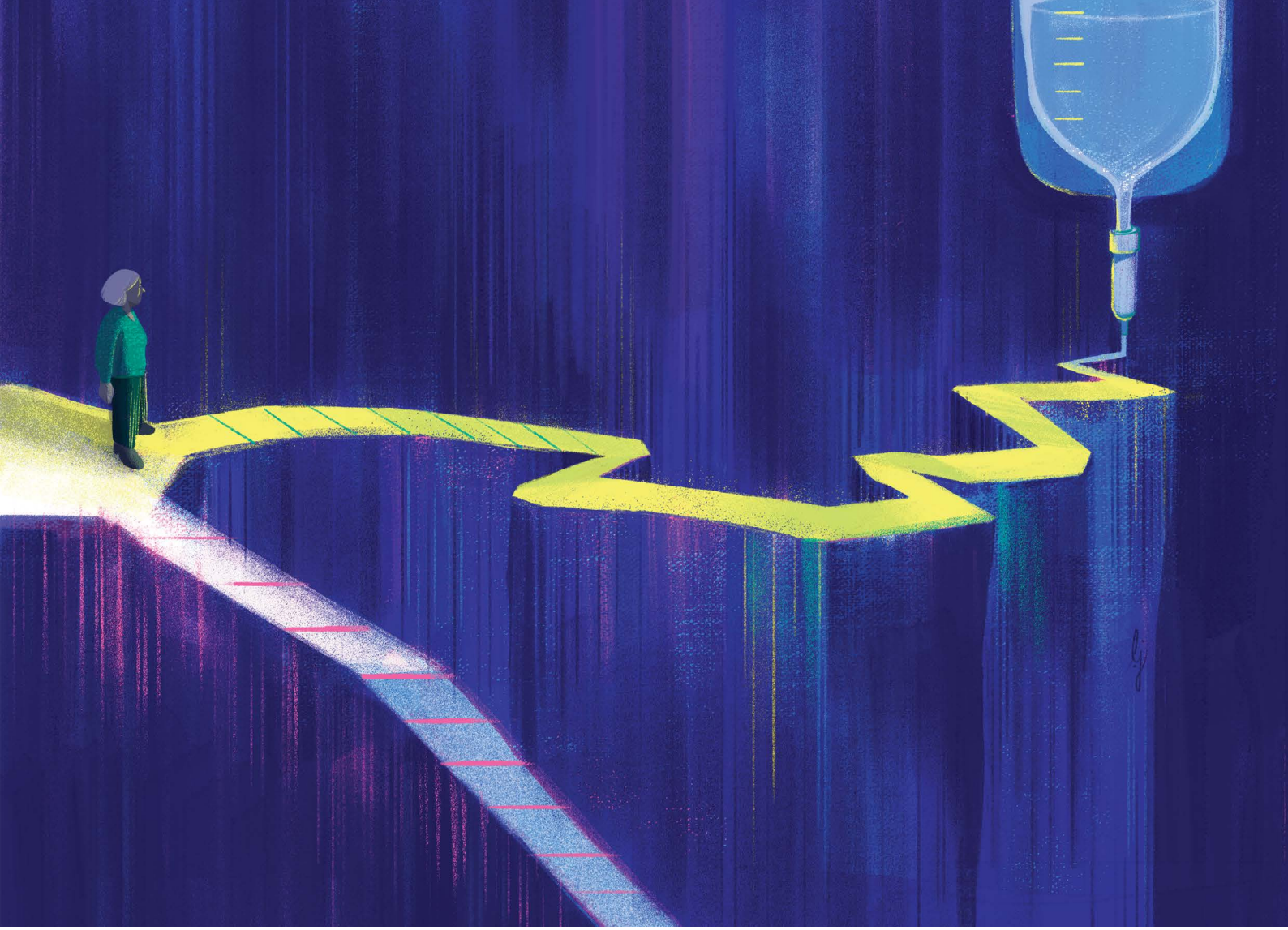
Aducanumab, marketed by manufacturer Biogen as Aduhelm, got the green light from the FDA under the agency's accelerated-approval pathway. It was the first medication to target, reduce and remove amyloid beta plaques. There was little evidence, however, that amyloid beta clearance correlated with slowed cognitive or functional decline. And the drug introduced the risk of ARIA, in addition to being riddled with other problems: controversial clinical-trial results, skepticism from the FDA's own advisory committee, an initial average annual price of $56,000, and refusal by the Centers for Medicare and Medicaid Services to cover the cost without additional clinical evidence of efficacy. Just 31 months after its approval, Biogen announced it was removing aducanumab from the market.

Since then, the FDA has approved two more anti-amyloid treatments: lecanemab (Leqembi), made by Eisai in partnership with Biogen, and donanemab (Kisunla) from Eli Lilly. Both slowed cognitive decline better than aducanumab or placebo in clinical studies. But both also come with a risk of ARIA. In the phase 3 clinical trial for lecanemab, which assessed efficacy and safety in large groups of people, about 9 percent of participants taking a placebo had brain swelling or hemorrhages, compared with 17.3 percent of those in the lecanemab group. In four separate donanemab trials, up to 30.5 percent of the participants showed brain abnormalities, compared with 0.8 to 7.2 percent in the placebo groups, and three deaths related to ARIA were attributed to the drug. Both therapies are also expensive—an average annual price of $26,500 for lecanemab or $32,000 for donanemab, plus hundreds to thousands more for required brain scans and other monitoring.

These therapies are not an option for everyone with Alzheimer's. They are recommended only for patients at early disease stages, and people most at risk for ARIA should avoid them. To identify the best candidates, D'Abreu and other neurologists put their patients through extensive cognitive assessments, costly positron-emission tomography scans to look for amyloid in the brain that would



help them diagnose the condition, and tests to determine whether they carry the gene variant *APOE* ε4, which increases dementia risk and the likelihood of brain swelling or bleeding in people taking anti-amyloid medications.

Despite the improved ability to assess risk, some neurologists remain highly dubious of available anti-amyloid therapies, as well as of the hypothesis they're based on: that amyloid is the root cause of the disease. James Burke, a neurologist at the Ohio State University Wexner Medical Center, was skeptical when lecanemab was approved in 2023 and says there still isn't enough clinical evidence to change his mind. Researchers have been collecting data beyond the 18-month time frame but currently have no good understanding of the drugs' longer-term effects.

Burke thinks it's important to draw a line between statistically significant changes, such as cognitive decline slowing by a reported 27 percent with a drug compared with a placebo, and those that are clinically meaningful, such as whether patients can drive safely or care for themselves with minimal assistance. "It's not obvious that people are even going to know the benefit is there," he says, but "the harms are very substantial and almost certainly badly underestimated." He notes that those harms, which include strokes and deaths that some attribute to the drugs, have occurred in rigorously controlled settings that do not necessarily reflect real-world conditions. Trial participants often are healthier and younger, on average, than typical dementia patients.

Burke is resigned, however, to the inevitability of prescribing anti-amyloid therapy for patients who meet the criteria. "If that's what they want, there's no point, for a provider who has access to treatment, in putting up a wall. They'll just get the treatment someplace else." But he also focuses on other approaches, such as helping people reduce vascular risk factors, eat a healthier diet and exercise more.

For now these drugs are the best pharmaceutical interventions on offer, says Judith Heidebrink, a neurologist and cognitive-disorder specialist at the University of Michigan Medical School. She was involved in the lecanemab phase 2 trial and its open-label extension. "Even given these risks," she says, those taking the drug are, on average, "more likely to maintain a higher level of independence and have slower disease progression."

That was what 80-year-old Bob Merriman was hoping for. He had seen both his parents and a brother ravaged by Alzheimer's. He knew his odds of developing it were high, and he desperately wanted to avoid the same fate. His wife, Mary, says he had signs of confusion and was getting easily frustrated with simple tasks.

Merriman reached out to his physician after hearing about anti-amyloid therapies and was referred to Heidebrink for evaluation. After extensive cognitive

testing, magnetic resonance imaging and blood work to determine whether he had cognitive impairment or a genetic predisposition to Alzheimer's (he did), Merriman began receiving biweekly infusions of lecanemab last November. He was willing to accept the potential risks and is checked regularly for signs of ARIA.

"He was determined," Mary says. "He was like, 'No, I know what the alternative is.'" She adds that he seems more focused than before and plans to continue taking the treatment for as long as possible. As anti-amyloid drugs edge into the mainstream, they are enabling additional research that can better predict who might be most susceptible to brain swelling and microbleeds, along with improved ways to find and manage potential risks. The result is increased confidence in these therapies among neurologists who might prescribe them.

Many patients who take lecanemab seem to share this confidence and, like Merriman, feel the drug helps them on some level. (Lecanemab has been on the market longer than donanemab.) D'Abreu and other neurologists say most of their patients choose to complete the initial 18-month course and often continue with maintenance therapy. That's helped sway D'Abreu's thinking on the medication, but she is not yet convinced of its efficacy. Because it's possible for patients with mild cognitive impairment to remain stable for months without treatment, she says she can't be certain how large a role anti-amyloid therapy plays.

Burke remains highly skeptical that the benefits of these therapies outweigh the risks. "This medicine can cause bleeding in the brain in one in 200 people," he says. "It's not a safe or benign medicine."

Fewer neurologists are sitting on Burke's side of the fence these days, however. More than two years after lecanemab was approved, overall hesitancy among practitioners in the field has shifted. In February 2024 market research firm Spherix surveyed 75 neurologists and found that fewer than half of them recommended lecanemab to their patients. They cited low satisfaction with the data and frustration with issues such as insurance coverage, logistics surrounding infusion access, and burdensome follow-up testing. A year later, however, 80 percent of those surveyed said they were now discussing anti-amyloid therapies with their patients. The average number of patients on lecanemab per surveyed neurologist has increased about fivefold. There are not enough data yet to gauge the acceptance of donanemab, which received full FDA approval in July 2024.

As the use of anti-amyloid medication becomes more widespread, there's also a need to better understand what happens when people on these therapies come into the emergency room experiencing a stroke or a blood clot, conditions that would usually be treated with drugs to induce thrombolysis, breaking up the clot. "Right now our data are incredibly limited, but there's a bunch of case reports of truly catastrophic bleeding when people are on amyloid-lowering agents and then get thrombolysis," Burke says. These concerns have become common enough that a report was recently published in *JAMA,* the most widely circulated medical journal, to help clinicians weed through the details.

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The hypothesis that amyloid beta is a root cause of cognitive decline is popular, and it's where the major drug companies have placed much of their focus. But it's not the only one, and controversy has plagued it for decades. It's been the subject of allegedly manipulated studies, and some assert academic institutions and government agencies have funneled research dollars to support this approach. The first positive results from aducanumab were preceded by a long line of failures.

Even ardent proponents of the anti-amyloid theory agree that additional methods for treating Alzheimer's are necessary. One idea is to use combination therapy, similar to how HIV or cancer drugs are administered, according to geriatrician Howard Fillit, co-founder and chief science officer of the Alzheimer's Drug Discovery Foundation. He says trials are underway for other therapies that target tau proteins in the brain, as well as inflammation and various metabolic pathways, all of which contribute to disease progression [see "A Multipronged Assault" on page S6].

There also are ongoing trials to determine whether anti-amyloid drugs administered before symptoms emerge can delay or even prevent the onset of Alzheimer's. The AHEAD 3-45 study, which comprises two trials, is testing whether the approach is effective against preclinical Alzheimer's—when amyloid plaque builds slowly and silently in the brain. If the amyloid hypothesis is correct and these clumps of protein are the primary cause of Alzheimer's, presymptomatic therapy could remove or prevent the formation of these plaques early on, thereby halting disease altogether. If the trials are successful, researchers may find that "we've actually delayed the inevitable clinical course for some of these patients," says Lon Schneider, a neurologist and gerontologist at the University of Southern California's Keck School of Medicine. The study should be completed in 2031.

D'Abreu's center at the University of Virginia is participating in a longer-term trial of donanemab, comparing the daily function of patients who are taking the drug versus those who are not. She still has concerns about the risks of anti-amyloid therapy, but as more data become available, she is increasingly comfortable about its safety and efficacy. More research could provide a more nuanced understanding of whether these drugs make a difference for patients and their care partners or whether the marginal improvement is not worth the untenable—and potentially lethal—burdens. D'Abreu remains cautiously optimistic.