NEUROSCIENCE

The memory race

Could a new model of testing and drugs make Alzheimer's disease as treatable as Type 2 diabetes? As researchers run trials to find out, doctors and patients are unsure about what to do for now

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PHOTOGRAPHY BY FRED LUM
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At a Toronto memory clinic, Tyson Haller waits for infusionist Sharanka Langstaff to prepare his dose for the AHEAD 3-45 study, a clinical trial of anti-Alzheimer's drugs.

Tyson Haller was in his early 50s when he learned he had a family history of one of the most feared diseases in medicine.

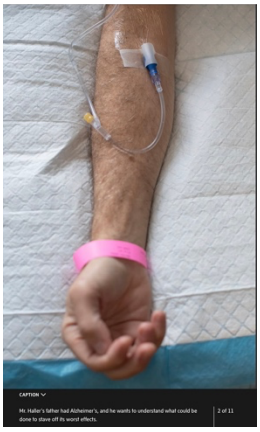
He and his older sister, Whitney Haller, made the discovery when they stumbled on the online obituary of their father, who left when they were

children. The notice said their Dad died in 2005 at the age of 75, “from complications resulting from a long battle with Alzheimer’s.”

That line nagged at Mr. Haller as he went about his busy days, dividing his time between working in the commercial office furniture business in Toronto and raising a son he welcomed late in life.

The trim and gregarious cycling enthusiast, now 60, thought about it whenever he forgot a name he should have remembered. He wondered if he was experiencing run-of-the-mill aging or the earliest signs of an illness that could siphon away his memories, leaving him a husk of the man he is today. He toyed with filming videos dispensing advice for his son while he was still himself.

“Because my father died of it, I said, ‘Is there a problem? A genetic mutation?’” he said. “I have a young son, so I wanted to understand everything I could do.”



Mr. Haller's father had Alzheimer's, and he wants to understand what could be done to stave off its worst effects.

Mr. Haller passed the standard visual and verbal tests without any hint of cognitive impairment, but given that those with a parent with Alzheimer’s are at an elevated risk of developing the disease, his physician agreed to refer him to the Toronto Memory Program.

The publicly funded neurology clinic diagnoses and treats Alzheimer’s and related disorders, as well as operating a large clinical trial unit.

There, Mr. Haller learned about the AHEAD 3-45 study, one of two major clinical trials for the prevention of Alzheimer’s dementia that experts are

watching with renewed optimism after two decades in which nearly every experimental drug for the disease failed.

AHEAD is not the first trial to test the theory that Alzheimer's is best combatted years before people become forgetful. But it is the first to try prevention with an FDA-approved, disease-modifying drug that has succeeded, albeit modestly, in slowing the progression of Alzheimer's in patients in early stages of the disease.

The thinking goes that if the drug, a monoclonal antibody called lecanemab, helped a little in those whose minds are already slipping, it might help a lot in younger people on firmer cognitive footing, like Mr. Haller.

Lecanemab, marketed as Leqembi, is part of a new class of drugs targeting beta amyloid. Sticky amyloid plaques are linked to brain-cell death. SUPPLIED BY EISAI VIA REUTERS

Lecanemab, sold under the brand name Leqembi, has been approved in the United States, Japan and China for patients with mild cognitive impairment or mild dementia owing to Alzheimer's disease.

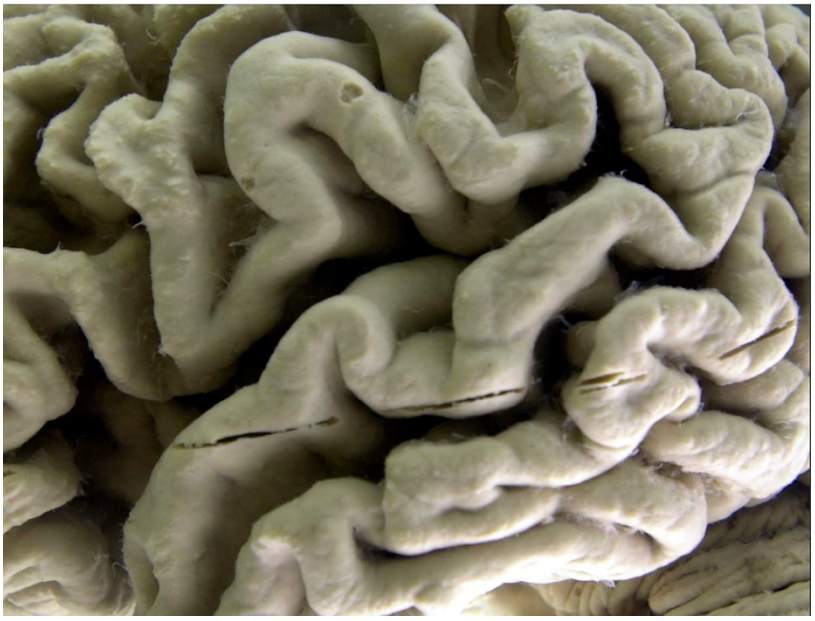
Regulators in Canada, Britain and Europe are expected to issue decisions this year on the drug, which was co-developed by U.S.-based Biogen Inc. and Japan's Eisai Co. Ltd.

Donanemab, a similar medication from Eli Lilly, which showed promise in early symptomatic Alzheimer's disease in a phase 3 study but has yet to be approved, is also being tested as prevention in a separate trial, TRAILBLAZER-ALZ-3.

Lecanemab and donanemab are part of a new class of treatments that could mark a turning point for Alzheimer's drug research, said Sharon Cohen, medical director of the Toronto Memory Program.

The intravenous medications target beta amyloid, a protein that congeals into sticky clumps in the brain, triggering a cascade of events that lead to brain cell death. There is an ongoing scientific debate about whether beta amyloid buildup causes Alzheimer's, but the plaques are a telltale biological feature that separates the disease from other causes of dementia.

"It is exciting to see disease-slowing drugs starting to have very substantial data," Dr. Cohen said. "For lecanemab, in particular, I was thrilled that the data was so strong and so consistent … everything was supporting the premise that if we tackle amyloid early, we can slow clinical disease."



Scientists have spent decades studying Alzheimer's-damaged brains like this one to see what remedies could work. DAVID DUPREY/THE ASSOCIATED PRESS

The modest success of the new anti-amyloid drugs in early disease and their use in prevention trials come at the same time as simple blood tests to diagnose Alzheimer's are proliferating in the U.S. Taken together, these developments mean that the dream of one day approaching Alzheimer's like Type 2 diabetes – by detecting it years early with a blood test and preventing or mitigating its symptoms with drugs and lifestyle interventions – is no longer a far-fetched fantasy.

But neither is it close at hand. The TRAILBLAZER and AHEAD prevention trials are slated to run until 2027 and 2029, respectively. That means that, for now, the Alzheimer's field is in a kind of purgatory. When used in people who are already symptomatic, the new anti-amyloid drugs don't stop the progression of Alzheimer's disease. They only slow it down. The treatments are also expensive and carry risks of brain microbleeds and swelling that require monitoring with frequent MRI scans.

"I don't think there's much question that the anti-amyloid drugs represent progress. The question is how much progress," said Howard Chertkow, chair in cognitive neurology and innovation at Baycrest Health Sciences in Toronto. "They're not a home run."

At this in-between moment, even defining Alzheimer's disease has become fraught. Pharmaceutical companies, eager for profits after collectively losing billions of dollars in the pursuit of failed Alzheimer's drugs, want the parameters set widely.

Doctors and patients also want to know: If prevention is plausible some time in the future, and diagnostic blood tests are already available in the U.S., how and when should Alzheimer's disease be diagnosed?

In the view of the U.S. Alzheimer's Association, patients with evidence of beta amyloid in their brain but no memory loss or cognitive decline already have "stage 1″ Alzheimer's disease.

In 2017, Sharon Cohen comforts her then 89-year-old mother, Donia Clenman, now deceased. Both of Dr. Cohen's parents and her grandmothers had Alzheimer's. Now, as medical director of the Toronto Memory Program, she works to avert a similar fate for other families.

Before the new generation of anti-amyloid therapies, Alzheimer's drug development was a wasteland of failure. The last drugs to be approved for the illness were greenlit two decades ago, and those medications only mitigated symptoms.

In the intervening years, at least 98 unique compounds tested in Phase 2 or 3 trials flopped, including one, solanezumab, that was tried as prevention. It failed to stop the accumulation of amyloid in the brain or slow cognitive decline in patients followed over four-and-a-half years.

Many of the dud compounds targeted beta amyloid, calling into question the "amyloid hypothesis," the theory that reducing amyloid plaques and their related tau tangles could slow or halt dementia caused by Alzheimer's disease.

"It was, in a word, agonizing," said Andrew Frank, a behavioural and cognitive neurologist at the Bruyère Memory Program in Ottawa. "I know in the breadth of human history, 10 to 15 years is not a long time. But when it comes to individual people and their families, 15 years is an eternity. So it was agonizing to watch the trials fail."

Those decades of disappointment help explain why Dr. Cohen of the Toronto Memory Program was buoyed by results of the lecanemab trials.

Dr. Cohen's clinic, where Mr. Haller is enrolled in the AHEAD trial, was one of the sites for an earlier trial of lecanemab in people with mild cognitive impairment or mild dementia due to Alzheimer's.

That phase 3 study, CLARITY-AD, found that lecanemab slowed the rate of cognitive and functional decline by 27 per cent compared to a placebo over 18 months. Patients on lecanemab declined 0.45 points less on an 18-point clinical dementia rating scale than those taking a placebo. The trial's secondary end points – other scales used to measure cognitive and functional decline – also showed significant disease-slowing, with functional decline slowed by 37 per cent.

In practical terms, that means people taking lecanemab can expect to retain their memory and thinking skills for about five months longer, on average, than would be the case if the disease ran its natural course.

Dr. Cohen holds her mother's hand. Even if lecanemab is not a cure, she says many families would jump at the chance to slow progression of Alzheimer's.

Dr. Cohen, whose late mother and father both had Alzheimer's disease, said that although lecanemab is not a cure, it could make a meaningful difference. "Most patients and families would say, 'that's a game changer for me. I can manage at this mild stage. What I fear is getting worse and being a burden on my family,'" she said.

Other experts are less impressed.

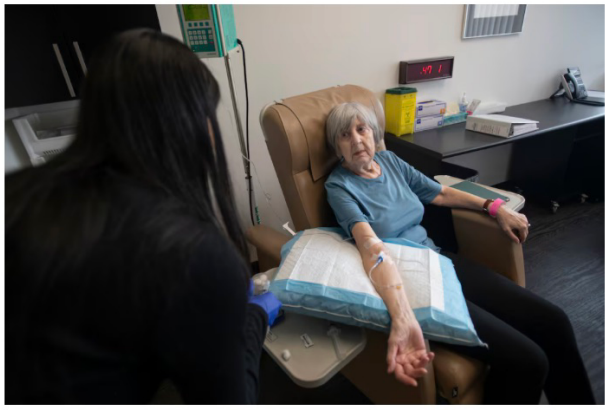
Dr. Chertkow of Baycrest, who is also the scientific director of the Canadian Consortium on Neurodegeneration in Aging, a national organization of dementia researchers, worries lecanemab's impact will be too subtle to notice. "With these drugs, the doctors won't be able to tell if they're working. The families may not be able to tell if they're working," he said. "We'll be taking the pharmaceutical companies' word and trusting them that the drugs work."

Still, the lecanameb results were more encouraging than the mixed findings of trials for aducanumab (commercialized under the name Aduhelm), another anti-amyloid drug that its maker, Biogen, abandoned in January after years of controversy and a congressional investigation that concluded the FDA approved it on weak evidence after a process that was "rife with irregularities," including inappropriate collaboration with Biogen.

Biogen withdrew its application to Health Canada for aducanumab in 2022, not long after the Canadian Consortium on Neurodegeneration in Aging and five other leading dementia research organizations urged the Canadian regulator to reject the drug.

Health Canada is still reviewing submissions for lecanemab, filed in May of last year, and donanemab, submitted in February, both for use in people with mild cognitive impairment or mild dementia due to Alzheimer's disease. Eli Lilly said recently that the U.S. FDA, which was expected to rule on donanemab in March, has asked a panel of independent experts to first take a second look at the evidence.

In the tests Mr. Haller took to be part of the AHEAD trial, he learned he has a genetic variation that increases his risk of late-onset Alzheimer's about tenfold.



One of the other participants in the study is 79-year-old Lynn Zimmerman, getting her infusion from the Toronto Memory Program's team leader, Byravi Sivasubramaniam.

When Mr. Haller decided to join the AHEAD trial, he underwent a battery of tests and scans that are unlike anything available to the average Canadian.

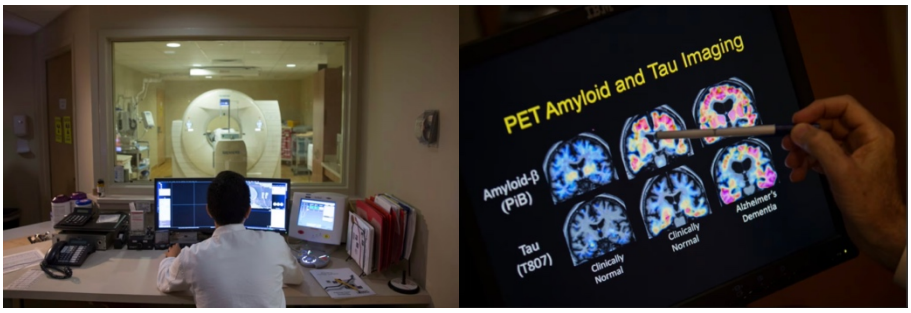
Right now, Canadian doctors diagnose Alzheimer's using visual and verbal cognitive tests, accompanied by a CAT or MRI scan and blood tests to rule out other causes of dementia, such as stroke or severe B12 deficiency.

Dementia, which affects an estimated 650,000 Canadians today, and Alzheimer's disease, are not interchangeable terms. The former is an umbrella term for loss of memory and thinking that impairs daily activities; the latter is its most common cause.

It used to be that Alzheimer's disease could only be confirmed at autopsy, when pathologists looked for the amyloid plaques and neurofibrillary tangles that German neuropathologist Alois Alzheimer first identified in 1906.

Today, amyloid plaques and tau tangles can be confirmed in the living using a PET scan or by testing cerebrospinal fluid obtained through a lumbar puncture. (Blood tests are coming but aren't yet used in Canada outside of research studies.)

Doctors in Canada don't routinely use PET scans or spinal taps to diagnose Alzheimer's because there's little point in confirming the presence of amyloid when there aren't any authorized anti-amyloid medications available. That would have to change if donanemab or lecanemab are approved.



PET scans allow doctors to find signs of Alzheimer's in living brains. EVAN VUCCI/THE ASSOCIATED PRESS

In Mr. Haller's case, his workup for the AHEAD trial included tests that revealed he has two copies of the APOE e4 gene, a variation that raises the risk of late-onset Alzheimer's (defined as striking after the age of 65) by about ten times, but does not guarantee he'll develop symptoms the way a rarer deterministic gene would.

Complicating matters further, patients with two copies of e4 have an elevated risk of amyloid-related imaging abnormalities (ARIA), anomalies visible on MRI scans that usually resolve without symptoms, but can be signs of microbleeds or swelling linked to anti-amyloid drugs.

All patients taking anti-amyloid drugs must be monitored for ARIA with frequent MRIs.

One analysis published in late 2021 predicted Canada would have the longest waiting times among G7 countries for accessing disease-modifying Alzheimer's treatments because the country already has lengthy queues for neurologists and MRI scans.

The drugs are expensive, too. Lecanemab sells for US$26,500 a year south of the border, a price private and public insurers in Canada would likely balk at.

"It's obviously a huge expense," said Jennifer Watt, a geriatrician-scientist at St. Michael's Hospital in Toronto and lead author of a recent commentary in the Canadian Medical Association Journal about the implications of offering the next generation of Alzheimer's drugs in this country.

She struggles with how best to use finite public money to care for people with dementia, many of whom can't afford basic help such as home care. "How would you want to spend those funds?" she asked. "On this drug that may or may not work, or on being able to live at home a lot longer?"

Whitney Haller, 61, drew the same genetic ticket as her brother, yet when she tried to join the AHEAD trial, the siblings discovered their paths had diverged. Spinal fluid tests and PET scans revealed he had enough amyloid plaque buildup in his brain to qualify. She didn't, despite being a year older.

Ms. Haller couldn't believe it. The news lessened her dread of Alzheimer's, but hardly erased it. She and her husband, who recently retired and have no children, know that her APOE status means they should put aside significant cash for dementia care at home or in an expensive facility.

"It is really difficult," Ms. Haller said. "We don't want to save all our pennies, and then nothing happens. And then we're sitting there at 75 and we're too old to really travel or go experience things."

Her brother, meanwhile, is trying to find a balance of his own while starting a new business outfitting commercial buildings with solar technology, sharing custody of his 14-year-old son, and visiting the Toronto Memory Program every two weeks for an infusion of either lecanemab or a placebo.

Whitney Haller still carries a genetic risk of Alzheimer's, but tests revealed she doesn't have enough amyloid buildup in her brain to qualify for a prevention trial. She says she and her recently retired husband are still figuring out what that means for their future.

While Canadians await Health Canada's rulings on anti-amyloid drugs, some Americans with mild cognitive impairment or mild dementia due to Alzheimer's disease are already receiving infusions of lecanemab.

Neurologist Suzanne Schindler and her colleagues at the Washington University School of Medicine in St. Louis are treating about 125 patients with the drug. The university's memory centre has expanded its capacity for lumbar punctures to collect fluid for amyloid tests, but Dr. Schindler expects the cumbersome procedure will soon give way.

"I think by the end of 2024 it is going to be extremely clear to everyone that the blood test can replace cerebrospinal fluid tests and amyloid PET in most patients for determination of amyloid status," Dr. Schindler predicted.

In the meantime, she added, there's a "Wild West" of lab-developed blood tests for Alzheimer's disease jockeying for primacy in the American market, some excellent, others "pretty bad." None has yet been approved by the FDA.

Leaders at the U.S. Alzheimer's Association felt the blood tests and new anti-amyloid drugs represented enough of a sea change that it was time to update the organization's criteria for diagnosing and staging of Alzheimer's disease.

A draft framework, unveiled at a meeting of the world's top Alzheimer's researchers in Amsterdam last summer, drew criticism for proposing that asymptomatic people with evidence of amyloid buildup in their brains be designated "stage 1" Alzheimer's patients.

The American Geriatrics Society called it "premature" to use that definition in a real-world clinical setting, emphasizing that many who fit the stage 1 criteria never develop dementia, often because they die of something else before memory and thinking deficits set in. (Earlier Alzheimer's Association guidelines referred to stage 1 as "preclinical" Alzheimer's for the purpose of research alone.)

Diagnosing people with Alzheimer's disease when they're asymptomatic could expose them to discrimination from employers or insurance companies, the AGS warned.

The AGS and others also denounced the Alzheimer's Association for ties to drug makers who stand to gain from diagnosing an untold number of seemingly healthy people with a dreaded disease. A third of the membership of the working group that wrote the new diagnostic criteria is employed by a pharmaceutical company. Another third has taken payments from the industry.

If disease-altering drugs are approved, Canada would need to rethink its practices for diagnosing Alzheimer's.

Critics of the new diagnostic criteria are missing the point, said Clifford Jack, an Alzheimer's researcher at the Mayo Clinic and chair of the working group.

He doesn't take money from pharmaceutical companies and said they didn't influence the group's recommendations.

The draft document, which isn't intended to be a clinical practice guideline, explicitly recommends against testing cognitively normal people for Alzheimer's biomarkers for now, except in clinical trials. Its purpose is to set out clear biological criteria for Alzheimer's disease that separates it from other causes of dementia, Dr. Jack said, and that must include defining its presymptomatic state.

Dr. Jack likens stage 1 Alzheimer's to certain cancers, diabetes, AIDS, and other diseases that tests can pick up early, before they make people visibly ill. "If someone with an HIV infection dies of some other cause, before they experience any AIDS symptoms, does that mean that HIV is not a real disease?" he said. "Of course not."

For Jason Karlawish, co-director of the Penn Memory Center at the University of Pennsylvania, "the question is, are we there yet?" – "there" being a place where cognitively well people with elevated amyloid levels should be diagnosed with Alzheimer's disease. "The answer is no," he said. "But we're getting close."

Dr. Karlawish, like many others in the Alzheimer's research field, hopes the final answer lies in the TRAILBLAZER and AHEAD studies. "But if those trials are negative, we'll be kind of left still scratching our heads."

Tyson Haller is doing his part to find answers. He visits the Toronto Memory Program regularly for his hour-long infusions. He suspects his IV bag is full of lecanemab, not a placebo, because early in the trial, as doctors ramped up his dose, he was hit with a short-lived bout of debilitating vertigo. But he can't say for certain.

As Mr. Haller continues to pass his visual and verbal cognitive tests, it has crossed his mind that speaking publicly about his risk factors for dementia due to Alzheimer's could imperil his business prospects. It's a risk he's willing to take for the possibility of delaying or preventing Alzheimer's disease – for himself and millions of others around the world.

"You got to do these things in life to help other people, right?" he said. "I've always been a big believer in science."

https://www.theglobeandmail.com/canada/article-alzheimers-lecanemab-ahead-clinical-trial/