Why so many health care professionals and scientists don't recommend Aduhelm to treat Alzheimer's disease

Many patients and caregivers have heard about Aduhelm, a drug that came onto the market in 2021 with the claim that it was the first "disease-modifying" treatment for people with Alzheimer's disease. (Its generic name is aducanumab.) But **an advisory committee of experts appointed by the Food and Drug Administration (FDA) voted overwhelmingly that it should not be approved. In January 2022, the Medicare program made an initial determination that it was not safe and effective enough to be covered outside of clinical trials – the first time that Medicare ever made such a decision about a prescription drug.**

The burden of Alzheimer's disease can be unbearable for patients, families, and the health professionals who care for them, so it's understandable that people would welcome any new drug claiming to help in this tragic condition. But the problem is that once all its clinical research studies are taken into account, Aduhelm does not appear to provide any meaningful benefit over an inactive comparison injection (placebo). Worse, **it creates worrisome swelling of the brain in 40% of patients given the recommended dose, and in some people that has progressed to bleeding in the brain.** That is why FDA's own advisory committee of outside experts made a nearly unanimous recommendation that the drug should not be given to patients.

The background story of Aduhelm helps explain why so many health professionals and scientists have decided that the drug should not be used outside of experimental settings.

Aduhelm was promoted as reducing an abnormal protein in the brain (amyloid), even though reducing amyloid levels has never been shown to benefit patients with Alzheimer's disease. The drug is not a tablet or capsule: **it has to be given every month as an intravenous injection in a doctor's office.** The drug company that makes it, Biogen, conducted two clinical studies to see whether the drug worked better than a placebo (inactive injection) in patients with Alzheimer's disease. **In 2019, the results of these studies were so poor that the company's data safety monitoring board concluded that it didn't work, and Biogen ended the clinical research early.** Most people assumed this was the end of the line for yet another drug that many had hoped could be an effective treatment for Alzheimer's disease, but which didn't measure up.

Then things took a surprising turn. The company noticed that in one of the two clinical trials, study subjects who were given a high dose appeared to have slightly less reduction in their memory and functioning after 18 months, though it was so slight as to likely not be noticeable by patients or their families. This difference was not seen in a second, very similar study. Biogen then had a series of official and unofficial meetings with the FDA to see if there was a more favorable way of interpreting their trial findings. Some of that unofficial contact is now being investigated by the agency's Inspector General. The company and some FDA staff proposed new ways of looking at the results of Biogen's

clinical studies that could put the drug in a more positive light. Over a year after the company had concluded that its drug was useless, it applied again to the FDA for approval, featuring a new way of analyzing the data from those same studies.

The FDA's own statisticians did not accept the idea that these new analyses showed that the drug actually helped patients. Neither did the panel of expert outside advisors that the FDA brought together to review all the information. That group included specialist doctors and scientists from around the country, chosen for their expertise in Alzheimer's disease and related areas. After reviewing all the information from the clinical trials, the advisory committee resoundingly agreed that the FDA should not approve the drug, because there was no convincing evidence that it helped the patients in the studies. The outside scientists were also very concerned that Biogen's data from the trials showed that **nearly half of the patients given the higher dose had swelling of their brains, which in some cases resulted in bleeding into the brain.** The FDA normally goes along with recommendations from its outside expert committees, but it is not legally required to do so. The FDA commissioner is allowed to overrule the recommendations of its advisory committee as well as its own staff.

And that is just what happened. Astonishing most observers, the acting FDA Commissioner moved the goalpost for the decision, and lowered the bar for what Biogen had to prove to get the drug approved. Instead of requiring that the drug had to be shown to help the memory loss and confusion caused by Alzheimer's disease, the acting Commissioner switched to a different set of rules; she decided that the company had to show only that it affected the levels of amyloid protein in the brain. The FDA initially approved the drug for use in all patients with Alzheimer's disease, including those with severe memory loss, even though the clinical studies had included only people with mild or early forms of the disease.

The law requires that if the FDA approves a drug based on a change in a scan or a lab test instead of actual patient improvement, the drugmaker must then perform a follow-up study showing that the medication actually helps patients. The FDA gave Biogen an unusually long period – a full nine years – to do that necessary follow up study, so that **the key information that patients and doctors need to understand whether the drug works will not be available for nearly a decade.**

Biogen immediately launched “patient awareness” websites. One asked people to answer questions to see if they might have early Alzheimer's disease. It asked about everyday occurrences like whether people sometimes forget where they put your keys or fell that it’s sometimes hard to find a word they’re looking for. If a person scored above a certain level, they were told to contact their doctor to see if they had Alzheimer's disease and what treatment would be available for them. One doctor noted that young, healthy research assistants in her lab took the test and many of them were told they might have Alzheimer's disease. Another Biogen-funded website offered to link people with doctors who could give them the drug, and places they could get the scans necessary for its use.

As soon as the drug was approved, Biogen astonished most doctors and patients by announcing that it would charge the average patient about $56,000 per year, a price that did not include the initial and followup scans necessary for its use, or the physician charges for giving the intravenous infusion treatments each month. Someone calculated that if most of the patients eligible to use the drug actually took it, **based on its initial price the country could end up spending as much on this one drug annually as it did to fund all of NASA each year.** In December 2021, Medicare officials did their annual re-calculation of premium costs to be charged to patients in the coming year, and concluded that **the expected addition of the cost of Aduhelm would contribute to the need to sharply raise the charge to patients for its Part B program from $158 to $170 per month; half of that increase was attributed to the projected cost of covering Aduhelm.**

The national drug evaluation authorities in Europe, Japan, and Canada refused to approve the drug. Besides initial decision of the Medicare program to cover the drug except for research purposes, many private insurers also decided not to cover it, and several well-respected medical centers have chosen not to offer it. These include the Cleveland Clinic, the Mount Sinai Hospital system in New York, Mass General Brigham in Boston, and many others. The FDA reconsidered its unfounded decision that the drug could be used in everybody with Alzheimer's disease, and scaled it back to cover only people with early disease, like the ones who were actually studied in Biogen's clinical trials. In December, 2021 a group of expert physicians and policy researchers from around the country called on FDA to withdraw Aduhelm from the market. On the same day, the company reconsidered the huge annual price it was charging and cut it in half.

But the damage was already done. **Sales of the drug have remained very low because so many physicians, patients, and families were not convinced that it worked,** and remain worried that the side effects of brain swelling and related problems that it cause were simply not worth risking. Another severe setback came in January 2022 when **the Medicare program made a preliminary decision that the information supporting the use of Aduhelm was so bad that it would not cover the drug except for patients in experimental settings.** It had never done that for any other drug. Medicare will finalize its decision in April.

Anyone who has ever cared for a person with Alzheimer's disease as a health care professional, family member, or other caregiver will feel disappointment over the failure of Aduhelm to live up to the hopes of so many. But it is never a good idea to adopt a new treatment – especially one that has important risks – just because other treatments are not good enough. It's important for patients and families to realize that if a doctor decides not to prescribe Aduhelm for someone with Alzheimer's disease, it isn't out of lack of concern, or stinginess. It is because the drug does not appear to work, and can cause important side effects. All of us concerned about this terrible disease must accept that for now, we are left with the same options we had before:

- make sure that a **careful medical evaluation** has eliminated the possibility of a different condition that can cause memory failure or confusion;

- use the **available non-drug approaches** that can help a person with memory failure cope with everyday life as well as possible:
    - a supportive environment;
    - the best possible management of other medical conditions;
    - behavioral interventions to maximize function;
    - exercise as tolerated.
- **Some existing older medications, such as donepezil and memantine, have weak effects** that patients and caregivers may nonetheless want to discuss with their health care professional.

Communities and organizations around the country do offer resources that can help people with Alzheimer's disease and their families. Some of them are listed at the link, "Resources for Patients and their Caregivers" at www.AlosaHealth.org .

Scientists in research labs around the world are working hard to discover a treatment that can actually deal with the terrible toll that Alzheimer's disease takes on its victims. It is likely that one day in the future, we will have such a treatment. But we don't yet, and **this ineffective, risky, and overpriced drug is certainly not a solution.**

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