

It is not clear whether new Alzheimer's drugs will make a difference at a population level, say researchers

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Cambridge researchers have cast doubt on whether new amyloid immunotherapy drugs will have the desired effect of significantly reducing the impact of Alzheimer's disease.

Writing in the journal *Alzheimer's & Dementia*, the team from Cambridge Public Health argues that substantial challenges including the risk-benefit ratio, limited eligibility and high cost of roll-out will limit any benefits of these treatments.

Alzheimer's disease is often quoted as causing 70% of the 55 million cases of [dementia](#) worldwide, though the definition of what constitutes the disease is hotly debated. One characteristic of Alzheimer's is the build-up of clusters of misfolded proteins, one of these being a form of amyloid, leading to plaques in the brain. The cascade hypothesis, a dominant theory in the field, suggests that this triggers a series of processes which together lead to dementia symptoms.

Advances in developing treatments to reduce symptoms and slow down the progression in the early stages of Alzheimer's have been slow. However, there has been recent excitement surrounding amyloid immunotherapy agents, drugs that harness the immune system to remove amyloid pathology.

Two completed phase III randomized controlled trials of amyloid immunotherapy reported statistically significant reductions in the rate of cognitive and functional decline compared to placebos.

But as the Cambridge team point out, the effect sizes were small—small enough that a doctor would struggle to tell the difference between the average decline of a patient on the drug and another on placebo, after 18 months. The drugs were also associated with significant adverse events, including brain swelling and bleeding; during the phase III trial of one agent, donanemab, there were also three deaths attributed to the treatment.

Crucially, there is little known about the long-term effects of the drugs beyond the 18-month trial periods. Long-term placebo-controlled trials,

which would be needed to see if there is any clinically meaningful slowing of decline, are unlikely to be feasible where drugs are already approved.

Despite this, the US Food and Drug Administration has licensed two such drugs. The European Medicines Agency (EMA) has recommended rejecting one (lecanemab) predominantly on the grounds that the small effects seen do not outweigh the risk from side effects; it is reviewing the other. The UK's Medicines and Healthcare Products Regulatory Agency (MHRA) is expected to take a decision on both drugs imminently.

Edo Richard, Professor of Neurology at Radboud University Medical Centre in Nijmegen, The Netherlands, and co-author, said, "If these drugs are approved by regulators in the UK and Europe, and become available, it is understandable that some people with early Alzheimer's will still want to try these drugs, given their despair living with this dreadful disease. But there is a lot of hyperbole around the reporting of these drugs, and significant effort will be needed to provide balanced information to patients to enable informed decisions."

Press coverage of the drugs has implied they are suitable for anyone with a diagnosis of Alzheimer's. However, while the trials included those with "early symptomatic Alzheimer's disease," it excluded those with other conditions that may have been contributing to their symptoms. Evidence suggests that the people in the trials represent less than 8% of those in the community with early Alzheimer's disease. Those in the trials were up to 10 to 15 years younger than those typically presenting to [health services](#) with early symptoms.

Lead author Dr. Sebastian Walsh, NIHR Doctoral Fellow in Public Health Medicine at Cambridge Public Health, University of Cambridge, added, "If approved, the drugs are likely to be relevant only for a

relatively small cohort of Alzheimer's patients, so potential recipients will need to undergo a range of assessments before being given access to the drugs. Plus, effect sizes seen in the trials are very small and the drugs will need to be administered as early in the disease process as possible, when symptoms are mild—and people in these phases of disease can be hard to identify."

The resource requirements for rolling out such treatments are likely to be considerable. Even if approved for only a small proportion of Alzheimer's patients, a much broader group of people will need to be assessed for eligibility, requiring rapid specialist clinical assessment and tests. The authors question whether this is the best use of these resources, given the existing strain on health systems. Support would also be required for the large number of Alzheimer's patients (potentially as many as 92%) found to be ineligible. Those found to have insufficient amyloid to be eligible may then require follow-up assessments to determine eligibility in the future, with the further implications for services this would entail.

Professor Carol Brayne, Co-director of Cambridge Public Health, said, "Even in high-income countries, rolling out such types of treatments at scale is highly challenging, but most dementia occurs in low- and middle-income countries. Health systems in these countries are highly unlikely to have the resources required to offer these new drugs, even to a very narrow group.

"Other compelling evidence suggests that attention to inequalities and health experience across people's lives could have greater impact on the rates of dementia in populations. Most dementia is more complicated than a single protein."

The team concludes that based on current evidence, it is far from clear whether amyloid immunotherapy can ever significantly reduce suffering

caused by dementia at scale in the community, and we must continue to explore other approaches.

Professor Brayne added, "With an aging population, we urgently need effective ways to support people living with dementia, but while the current amyloid immunotherapies may show a glint of promise for very selected groups, it's clear these drugs will not address dementia risk at scale."

More information: S. Walsh et al, Considering challenges for the new Alzheimer's drugs: clinical, population, and health system perspectives, *Alzheimer's & Dementia* (2024). [DOI: 10.1002/alz.14108](https://doi.org/10.1002/alz.14108)

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