Alberta Doctors' Digest

Are lifestyle changes more effective than potential new Alzheimer's drugs?

Alzheimer's disease (AD) is the most common form of dementia; it affects 10% of people over the age of 65. Despite having been discovered over 100 years ago, there has yet to be an effective cure. Instead, between 2000 and 2012, 99.6% of drugs tested in clinical trials for AD failed, which is a higher fail rate than cancer trials.

There are several reasons for the difficulty in finding a cure:

- Etiology of AD is still unknown.
- Most of our animal models are based on the familial variant of AD, which accounts for only 10% of total cases.
- While we think that amyloid and tau may play a role in the pathology of the disease, it is unclear if targeting these biomarkers can slow or reverse AD.
- The relationship of amyloid and tau to cognitive decline has always been in question (see the famous nun study).
- High interpatient heterogeneity.
- The fundamental inaccessibility of the brain for routine testing.

With the global population getting older, Alzheimer's disease will become more prevalent, and a treatment is desperately needed. (Photo image credit: Mabel Amber, Pixabay.com)

With the global population getting older, AD will become more prevalent, and a treatment is desperately needed. This creates a temptation to take shortcuts and accept even the smallest glimmer of hope. Aducanumab and lecanemab are two new AD monoclonal antibody therapies from Biogen which have received accelerated approval – but not without controversy. Biogen withdrew its application for aducanumab from Health

Canada in June 2022 after approval by the FDA one year prior, but it is worth revisiting the issues surrounding this drug and seeing whether the process of Alzheimer's drug approval has improved.

Aducanumab was approved in June 2021 under the FDA accelerated-approval pathway and was heralded as the first newly approved AD drug in 20 years. However, there was significant disagreement surrounding this approval. Firstly, the efficacy of the drug was on the basis of two discontinued Phase III clinical trials (EMERGE and ENGAGE), one of which (ENGAGE) showed no difference in efficacy between the treatment and placebo. Secondly, an external review panel comprised of nine scientists and neurologists hired by the FDA near unanimously recommended against the approval of aducanumab. However, the drug was still approved. Thirdly, aducanumab was originally priced at over $50,000/year, but after numerous objections and many public health agencies being unable to pay for such an expensive product, Biogen dropped the price to $28,200/year. Finally, in December 2022, the US House of Representatives released a report finding that the interactions between the FDA and Biogen regarding the approval of aducanumab were "atypical," "failed to follow the agency's own documentation protocol" and "inappropriately collaborated on a joint briefing document for the [Peripheral and Central Nervous System Drugs] Advisory Committee that did not adequately represent differing views within FDA." However, no penalties were given to either the FDA or Biogen.

In the present day, the situation does not appear to have improved. Lecanemab was approved for the accelerated-approval program in January 2023 after the first Phase III trial, CLARITY-AD, showed a statistically significant mean change in the clinical dementia rating sum of boxes (CDR-SB) score after 18 months compared to placebo. Although the results of the trial are more straightforward than those of aducanumab, lecanemab is not without criticisms. During the trial itself, consent forms were changed midway after several deaths were linked to concurrent blood thinning agent and lecanemab use, although it was previously stated that there was no associated increased risk with concomitant use.

Even though it is normal for unexpected adverse events to become apparent when larger Phase III trials are initiated (compared to the relatively smaller Phase II trials), the decision to grant accelerated approval status in this case, especially after the previous issues with aducanumab, has drawn scrutiny. Additionally, unlike with aducanumab, there was no external advisory committee input prior to this approval. Overall, there does not appear to have been much done towards regaining trust from the medical community during this second attempt at an AD disease-modifying therapy.

But perhaps the most overlooked issue is whether these drugs actually show clinical benefit. Looking at the primary endpoints, the EMERGE trial showed a -0.39 change in CBR-SB score, while the CLARITY-AD trial showed a -0.45 change in CBR-SB score after 18 months compared to placebo. These results were both statistically significant, but how important is this in the real world? For the CBR-SB, a change in one to two points is considered clinically meaningful. The main issue with these drugs remains in plain sight: it's not clear that they will substantially change the course of disease.

So, what do we tell our patients? How do we balance the urgent need for Alzheimer's treatments and the need to perform laborious, slow but thorough, science-driven investigations? Although there is yet to be a cure, several clinically relevant and effective

disease-modifying treatments are already shown to slow down disease progression or development of AD.

- A meta-analysis of 214 studies found that high systolic blood pressure increases incidence of AD by 11% while another meta-analysis found that anti-hypertensive use in adults >40 years old with hypertension has a 0.94 relative risk of AD compared to non-antihypertensive use.
- Physical activity has been found to be associated with decreased risk of all-cause dementia (RR=0.80), Alzheimer's disease (RR=0.86) and vascular dementia (RR=0.79).
- Current smokers have a 30% increased risk of dementia, 40% increased risk of AD and 38% increased risk of vascular dementia compared to those that have never smoked. Importantly, smoking cessation reduced the risk of dementia to that of those who never smoked.
- A 10-year longitudinal study found that people engaged in cognitively and socially stimulating activities were less likely to develop dementia by 58% and 71% respectively.

Although none of these lifestyle changes are guaranteed to protect people from dementia, they are affordable and highly investigated recommendations, have minimal side effects, and are not marred with scandal and questionable ethics. For a multi-factorial disease such as Alzheimer's, a multi-factorial solution is needed.

Editor's note:

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