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Commentary

Under-Represented Populations Left Out of Alzheimer's Disease Treatment with Aducanumab: Commentary on Ethics

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Abstract. Despite controversy about the efficacy and safety of aducanumab, the FDA's fast-tracking of this medicine is truly historic. However, structural problems leading to socioeconomic disparities and systemic racism in science, healthcare, and society have left out under-represented populations. This perspective outlines the racial and socioeconomic health disparities in aducanumab treatment: 1) Disparities in the risk of Alzheimer's disease (AD), 2) Limited participation from under-represented groups in AD trials raising concerns about the generalizability of the results, 3) Questionable applicability of the amyloid hypothesis in groups under-represented in AD research, and 4) Aducanumab's initial sticker price that unfairly singled out those with lower socioeconomic backgrounds. Potential solutions are discussed.

Keywords: Aducanumab, Alzheimer's disease, bioethics, ethics

Alzheimer's disease (AD) is the most common dementia in older adults. AD dementia is highly debilitating and affects almost six million people in the US alone. Unfortunately, the five FDA-approved AD medications have not been shown to stop or reverse the disease process. In contrast, aducanumab is believed to be a disease-modifying drug that works towards slowing AD progression by reducing amyloid-β (Aβ) buildup in the brain. It was approved by the FDA in June 2021 [1]. Given mixed reviews from the FDA advisory committee, the Office of Neuroscience and statisticians about the efficacy and safety of aducanumab, the FDA's approval of this medicine is truly historic [2]. The approval of aducanumab was based mainly on two phase III, randomized, double-blind, placebo-controlled trials in patients with early AD (ENGAGE and EMERGE) [2]. These studies were sponsored by Biogen and were conducted at 348 sites in 20 countries. Participants ($n = 3{,}285$) with early AD (MCI due to AD or mild AD dementia) were recruited. Only one of the two trials (EMERGE) supported the benefits of the drug (reduced clinical decline) while the other showed no difference in outcomes [2]. However, both studies reported a dose-related side-effect of brain edema, an amyloid-related imaging abnormality (ARIA) [3]. Thus, the trials were stopped.

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Following this decision, the trial investigators re-analyzed as more data were collected, and they conducted sub-analyses using other outcomes in those with and without the life-threatening side-effect. The drug was then approved by the FDA [1, 4].

In addition to the efficacy and safety concerns, several ethical concerns in the testing and use of the drug must also be brought to light. Structural problems, such as disparities in socioeconomic status and systemic racism in science, healthcare, and society, have left under-represented populations out of this historic treatment in several ways. First, there are clear disparities in the risk of AD [5, 6]. Second, only a limited number of participants in the aducanumab phase III trials were from groups under-represented in AD research, bringing up concerns about the generalizability of the results [3]. Third, the amyloid hypothesis may not explain the cause of AD in under-represented populations, thus calling into question if aducanumab is the right medicine for groups under-represented in AD research. Fourth, and perhaps the most pragmatic barrier, is the high sticker price of the drug that unfairly singles out those with lower socioeconomic backgrounds.

DISPARITIES IN THE RISK OF AD

Under-represented populations, such as certain racial/ethnic groups and people from under-resourced communities, have disproportionately high rates of AD. Compared to older white Americans, older Black and Latinx Americans are about two and one and half times, respectively, more likely to develop AD [5, 6]. Although Black Americans make up only 14% of the US population, they bear one-third of the costs associated with dementia [7]. By 2060, the number of Black Americans living with AD will be doubled, and the number of Latinx Americans living with AD will be quadrupled [8]. Disparities in health conditions (cardiovascular disease and diabetes), socioeconomic status (lower education, high rates of poverty), and life experiences may explain some of the differences in the risk of AD for certain racial/ethnic groups. Furthermore, societal factors may predispose all racial/ethnic groups living in under-resourced communities to an increased risk of AD and poorer outcomes by influencing where they live, the education they receive, the jobs available to them, and the healthcare that they can access. Yet, AD research continues to elude the study of these under-represented groups.

UNDERREPRESENTATION OF CERTAIN POPULATIONS IN AD RESEARCH

Throughout history, Black, Latinx, and Indigenous groups in the US have been underrepresented in clinical trials. For example, the A4 study (Anti-Amyloid in Asymptomatic Alzheimer's Disease), one of the largest dementia prevention trials, has less than 8% participation of under-represented racial/ethnic groups [9]. Moreover, although some of these patients were Asian participants recruited in sites in Japan, the majority of participants in the A4 study were recruited in US sites [9]. While the reasons for such an imbalance of participation in research vary—income barriers, medical mistrust stemming from historical instances such as the mishandling of Black participants in the Tuskegee syphilis experiment and Henrietta Lacks's cancer cells [10, 11], bias of professionals when choosing participants, lack of access to resources, and health/research literacy—the consequences remain the same [12, 13]. Of the 3,285 participants in the aducanumab studies overall, less than 14% constituted under-represented populations [3]. The study's population does not parallel the diversity of the US population, nor does it reach the target populations of those most affected by AD.

REASONS WHY ADUCANUMAB MAY NOT BE THE RIGHT APPROACH IN GROUPS UNDER-REPRESENTED IN AD RESEARCH

There are many instances in research that highlight the need to study the etiology and treatment of diseases specifically in under-represented populations. For example, common medications used to treat high blood pressure, such as beta blockers and angiotensin-converting enzyme inhibitors, work well among white patients but do not work so well for Black patients. This is because Black populations have a higher prevalence of hypertension (28.4%) than any other racial/ethnic group, leading to worse prognosis, and exhibit different pathophysiology, meaning the drugs mentioned above will not work as effectively [14]. Similarly, there is emerging data that the *APOE4* gene, the most studied genetic risk factor for AD, may not confer the same risk of developing AD among Latinx people [15]. Importantly, tau protein was shown to be a better biomarker of AD than Aβ in a community-based study of multi-ethnic participants, suggesting the

amyloid hypothesis on which aducanumab treatment is based may be less relevant for certain populations [16]. Hence, it is important to conduct well-powered studies to test the efficacy of aducanumab if the goals are not only reducing plaque burden but improving quality of life and prognosis in those from diverse racial/ethnic and socioeconomic backgrounds.

FINANCIAL BARRIERS

Initially, aducanumab treatment overall was priced very expensively at $50,000. This did not include the hospital care required for the monthly infusions, transportation, extra caregiver time, or even the need for serial magnetic resonance imaging (MRI) scans to check for brain swelling. After a public outcry around the costs to the healthcare system, the company reduced the cost by 50%. Even after the cost reduction many patients would have been unfairly left out of the historic AD treatment, especially those from under-resourced communities. Ultimately the drug was made available at low or no cost if patients agreed to be part of a clinical trial. Patients at the intersection of lower socioeconomic status and under-represented racial/ethnic group will require the most attention to ensure equity of access, even if we find aducanumab to be equally effective for them.

PROPOSED SOLUTIONS

Racial and socioeconomic health disparities have always been prevalent in the fields of medicine and research in the US. It is important to break down the barriers that prevent under-represented (racial/ethnic and lower socioeconomic) groups from participating in research and receiving the same treatments. For under-resourced populations to afford aducanumab, economic strategies such as targeted discounts in treatment cost, discounted MRI costs, and paid caregiver services are urgently needed. The Centers for Medicare & Medicaid Services (CMS) has announced recently that Medicare will cover the cost of aducanumab treatment, and this will alleviate some concerns but might also increase monthly Medicare Part B premiums.

The FDA requires Biogen to verify the clinical benefit of aducanumab in a post-approval trial. It is important that under-represented populations be well-represented in the post-approval trials. A massive public health campaign and concerted efforts by public and private sponsors of research are needed to overcome the barriers to participation by under-represented populations in research. Some strategies to improve participation by under-represented populations include 1) funding agencies starting to enforce existing requirements for inclusion, 2) increasing diversity in the research workforce, 3) enlisting trusted community organizations, 4) deploying endorsements from culturally concordant providers and celebrities, and 5) treating under-represented participants equitably. One successful approach to breaking down institutional mistrust is the promotion of scientists from under-represented populations. Dr. Kizzmekia Corbett, one of the key scientists behind the development of the Moderna COVID vaccine, was recently named one of the *Time*'s Heroes of the Year [17]. She has participated in several town hall meetings to discuss the development of the vaccine in efforts to reduce vaccine hesitancy among under-represented groups of people. Efforts such as these could potentially be useful for the study and use of aducanumab in the future.

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The authors have no conflict of interest to report.

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