VIEWPOINT

What the Aducanumab Approval Reveals About Alzheimer Disease Research

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The US Food and Drug Administration (FDA) recently provided accelerated approval for aducanumab to treat Alzheimer disease (AD). The decision was controversial within and outside the FDA because of inadequate evidence of medication efficacy. The Peripheral and Central Nervous System Drugs Advisory Committee voted against recommendation of aducanumab and several committee members resigned after approval. FDA approval was based on trials that were not inclusive of the people who bear a disproportionate burden of disease.[1] Only 0.6% (ie, 19 individuals) of participants identified as Black, 3% as Hispanic, 0.03% (1 person) as American Indian or Alaska Native, and 0.03% as Native Hawaiian or Pacific Islander. Of the 9% identified as Asian, 94% were recruited in Asia.[2] Older Black adults are estimated to have AD incidence up to double the rates in older White people. Despite this, Biogen reported that only 6 Black people were randomized to the treatment dose approved by the FDA.

Why should there be concern about inadequate representation of people from historically excluded racial and ethnic backgrounds in AD clinical trials? Because the safety and efficacy of treatments among a narrow subgroup of people cannot be assumed to generalize to other groups. We focus on underrepresentation of Black people in aducanumab trials, but identical arguments hold for numerous other groups for whom safety and efficacy may vary.

Racial categories are sustained by social norms and policies that shape nearly every dimension of life. These phenomena—interlocking to create systemic racism—drive racial health inequalities[3] and may influence preclinical biomarkers, medication adverse effects, and medication efficacy. As a result of exposure to interpersonal and structural racism throughout life, older Black people are more likely than White people to have hypertension and diabetes, to experience ischemic and hemorrhagic stroke, and to have white matter hyperintensities.

The omission of Black patients from the aducanumab trials is particularly troubling given these racial health inequities. Vascular disease may exacerbate the common adverse events attributed to aducanumab, including microhemorrhages and vasogenic edema, ie, amyloid-related imaging abnormalities (ARIA). People with recent strokes or transient ischemic attacks were excluded from the trials, presumably for safety considerations, but these are not contraindications to prescription on the FDA-approved medication label. Adverse events were also far more common for *APOE e4* allele carriers. Most research indicates that—compared with White individuals—*APOE e4* is more common, although less strongly associated with AD risk, in Black individuals. These factors elevate the plausibility that ARIA may be more common in Black people, but our concerns are entirely speculative, because there is essentially no information on outcomes among Black people.

Despite this lack of evidence, the Alzheimer Association has called for access to aducanumab for all patients affected by early AD.[4] The makers of aducanumab, who apparently did not consider it necessary to include Black people in the evaluation of medication safety and efficacy, now consider it essential to include Black people as paying customers. The demand for equal access conveniently creates pressure for Medicare and Medicaid to provide coverage for the medication's $56 000 annual price tag. Others have discussed the potentially devastating impact of such expenditures on Medicare[5] and the missed opportunities to fund resources established to benefit people living with AD.

Despite potential harms to public health, calls for equitable access or early identification seem beyond reproach, incentivizing others to collaborate with Biogen. Publishers of the Montreal Cognitive Assessment (MoCA), a screening test that differentially misclassifies Black people as having cognitive impairment,[6] recently partnered with Biogen because now, "early detection is more important than ever." CVS is rolling out free cognitive screening to "increase access to Aduhelm."[7] Biogen's recently launched advertising campaign includes a cognitive symptom quiz: regardless of the responses, quiz takers are advised to discuss cognitive screening with their physician.[8] These campaigns harken to industry-sponsored efforts in other diseases—expand the definition of the disease, increase diagnoses of asymptomatic individuals, and increase the number of people receiving treatment—regardless of clinical benefit.[9]

Ensuring that access to high-quality medical care does not differ by race, ethnicity, or ability to pay is an obvious moral imperative. But aducanumab creates a dilemma. The medication has no proven clinical benefit and has demonstrated adverse effects for White people that may plausibly be worse for Black people. The current price of aducanumab will entail major sacrifices for families: even with 80% Medicare coverage, the remaining cost equates to 24% of median household wealth among Black older adults.

Neither clinicians nor the public should face this dilemma. FDA approval was the final step in a series of failures; it is now the responsibility of the AD research field to critically reflect on the forces that led us here, and to restructure the system to avoid repeating these mistakes. Inclusion is a cornerstone of rigor; noninclusive trials are operationally flawed. AD trial exclusion crite-

ria often differentially exclude Black participants but even these possibly overly conservative exclusion criteria cannot explain the extreme underrepresentation of Black individuals. Designing trials that can establish safety and efficacy for people who are disproportionately burdened by the disease should be required for FDA approval.

Lack of evidence among Black populations in AD biomarker research reflects decades of disregard for inclusion. AD and AD-related dementia biomarker studies often purport to be race neutral, but center White people. As a result, we have limited information comparing the sensitivity and specificity of biomarkers for clinical outcomes in Black and White individuals. The prior science used to justify amyloid as a surrogate outcome for AD, including the research framework for a biological definition of AD,[10] was not inclusive and therefore not rigorous. Why was such incomplete science accepted? Why did the authors of the research framework, including a Biogen executive and an FDA official, consider the experiences of non-White individuals unnecessary when defining biomarker criteria for AD?

Many patients will assume that FDA approval implies a medication is safe, and will trust that their physician has reviewed evidence showing that people like themselves tend to benefit from therapy. Aducanumab approval, based on treating only 6 Black patients, makes it impossible for physicians to honor this trust. Researchers and clinicians may claim that Black people's participation in research is a priority, and that providing appropriate treatments to Black patients is a nonnegotiable criterion for high-quality care. Approval of medications without evaluating safety and efficacy in Black patients belies such claims. The decision to approve aducanumab, assessing the evidence including only 6 Black patients as sufficient, reveals the low priority given to Black trial participants and the health of Black people. Safety and efficacy evidence among representative populations should now be the top priority for both researchers and advocates.

The experience with aducanumab may soon be repeated with other medications. Approving and advocating for medications with inadequate evidence of safety and efficacy is dangerous, erodes trust, and further entrenches nonrepresentative research norms. Inclusion is achievable when it is prioritized and collaboratively planned. The Equity in Neuroscience and Alzheimer Clinical Trials (ENACT) Act (S 1548/HR 3085) would incentivize diverse representation and require community-based engagement in AD trials. The legislation does not apply to industry, however, and would not govern clinical research that must precede trials. A culture change is needed, so that everyone, not just disparities researchers, but all scientists, all advocates, and all health care professionals, insist on inclusive research. AD studies that do not represent the diversity of humans affected by AD should no longer be acceptable.

ARTICLE INFORMATION

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