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Title Page

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Commentary Making the Case for the Accelerated Withdrawal of Aducanumab

The U.S. Food and Drug Administration's (FDA) approval of aducanumab (Aduhelm® in the US) as a treatment for Mild Cognitive Impairment (MCI) of the Alzheimer Type and Alzheimer's Disease (AD) has raised such major concerns about efficacy, safety, FDA processes, and regulatory capture that Biogen's license to market this biologic should be immediately withdrawn. Aducanumab has not demonstrated benefit to patients, failed to meet regulatory guidelines, and is likely to cause both individual and societal harm. The FDA approval process—particularly the inappropriate use of its accelerated pathway—needs to be heavily scrutinized. Lay advocacy groups (e.g., the Alzheimer's Association, USAgainstAlzheimers and others) and dementia experts themselves also need to reflect upon their roles in this debacle. The question we must answer is how to prevent such regulatory and scientific lapses so we can protect and improve the quality of lives of people with dementia and their families.

**Background**

Aducanumab was granted market access by the FDA in June 2021 through the Accelerated Approval process after failing standards for regular approval. The manufacturer Biogen had conducted two clinical trials, both of which were stopped early for futility and only one of which showed statistically significant but not clinically meaningful differences. The drug received a negative appraisal by the FDA's statistical team and has significant unresolved safety issues. The FDA had instructed its Advisory Committee in November 2020 not to consider the biomarker data, but instead to focus on the clinical endpoints. Subsequently, the drug was voted down unanimously (with one abstention) for regular approval because the clinical data was deemed insufficient.

The senior leadership of the agency then decided to shift aducanumab into an accelerated pathway, where the drug was approved based on PET imaging of amyloid beta plaques, a controversial and unvalidated biomarker. Three members of the advisory committee resigned in protest, and personal conversations indicate they would not have supported accelerated approval[1,2]. The "amyloid hypothesis", i.e. the embattled theory that amyloid-related proteins are the cause of cognitive impairment, has long dominated Alzheimer's research and appears to have motivated the approval.

**Arguments to withdraw**

The principal reason to withdraw aducanumab is that neither actual nor expected clinical benefit was demonstrated. Various post-hoc analyses were conducted by the FDA and Biogen to try to explain the one failed randomized clinical trial, effectively basing the decision to approve on the assumption that the positive study was the right one. Available evidence suggests that PET amyloid imaging does not predict clinical benefit, and this was known or should have been known, prior to the approval decision[3,4].

Safety remains a significant issue, as brain edema or microhemorrhages occurred in 41% of patients getting the recommended dose in closely monitored trials of relatively healthy participants. Brain volume loss of uncertain importance also occurs. Yet the FDA labeling lists no contraindications even though people with vascular risk factors and history of stroke and other pathologies were excluded in

the FDA submitted trials (not to mention minority groups with different risk-factor profiles). Since approval, at least one death seems to be associated with aducanumab.

In addition to posing a real risk of harm to patients, aducanumab comes with huge potential societal costs. Biogen quickly announced a "fair" annual price of $56,000 (now reduced to $28,200), far exceeding expectations. In addition, imaging (which is not required by the FDA package insert), the costs of infusion itself, possible genetic testing (with complex and uncertain implications), and other administration costs will increase the price substantially. Immediately, healthcare providers, including the Veterans Administration, announced they would not administer, and payors declared they would not pay for the drug. CMS began a process of reviewing national pricing. To cover the anticipated costs of this one drug, CMS announced one of the largest rises in Medicare Part B premiums in the history of the program. Globally, the financial stakes are even more astronomical, depending upon how therapeutic targets are defined. Both so-called Mild Cognitive Impairment and the Alzheimer's syndromes are subject to different definitions and hence lead to different cost estimates. In the US alone, paying for aducanumab could run into the billions of dollars per year—all for a drug that has not been shown to offer meaningful clinical benefit.

**Larger issues at stake**

The most common argument against calling for the withdrawal of aducanumab is that the drug will die by other means, such as market competition from other drugs, refusal of reimbursement, or for safety reasons, which amounts to waiting for patients to be harmed. Others believe that calling for withdrawal amounts to discrimination against older people with cognitive problems; that experts should not challenge the FDA; that "appropriately" educated patients should be able to decide for themselves; or that paying for aducanumab will support chronically underfunded memory clinics. Unspoken are potential fears of the dominant organizational forces that pushed for approval and the potential adverse impact on funding and their own professional reputations and careers. We reject these arguments.

The approval of aducanumab raises questions about the appropriateness (some might say coziness) of interactions between the FDA, industry, and patient advocacy groups[5]. In recent years FDA staff collaborated with Biogen in publishing papers that promoted Alzheimer's as a biomarker-defined condition. Frequent meetings between Biogen and FDA are now being investigated by the Inspector General. The Alzheimer's Association, which, in briefings to volunteers and the scientific community took considerable credit for approval, had meetings with the FDA between the convening of the advisory panel and the agency's final decision. Additionally, the Alzheimer's Association, and other groups have based fundraising efforts around false hope of "ending Alzheimer's Disease" by 2025 and have portrayed aducanumab as being the first step in unleashing a wave of innovation in the field.

Equally important is the question of who is being served by the accelerated approval process, patients and the public, or industry? The surrogate endpoints used for accelerated approvals consistently underemphasize harms and have often been shown not to predict clinical benefit when follow-up trials are done[6]. Aducanumab will likely allow similar drugs to slide under the lowered evidentiary bar.

**Conclusion**

The vast sums of money that might be spent on this drug and others that fail to demonstrate minimally clinically important differences could be spent elsewhere with far greater effect[7]. Focusing on promoting cognitive/brain health, supporting caregivers, community programs involving exercise, the arts, and

other forms of engagement, and lowering exposure to neurotoxins like lead and air pollution particulates would be wiser investments. Mitigating climate crisis associated environmental degradation and disasters would actually improve the quality of life of all of us at risk for age-related cognitive challenges.

We believe the lessons of the disastrous approval of aducanumab are too important to ignore. The Alzheimer's field is premised on many contested ideas (most principally that Alzheimer's is a single condition unrelated to aging and amyloid is a causative agent), and unrealistic expectations of imminent cure. Biomarkers require validation to be clinically valuable. If we just focus on the biological aspects of illness, we risk not putting patients and communities first. If we also focus on transforming healthcare, including Long-Term Care, and protecting our ecosystems, the lives of those with cognitive challenges today and tomorrow (perhaps all of us) would be enhanced.

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