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What Might Aducanumab Teach Us About Clinicians' Judgment About Whether to Recommend Emerging Alzheimer's Interventions?

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Abstract

Alzheimer's disease (AD) is an incurable, progressive deterioration that ends, eventually, in death. For many years, AD's hallmark etiological feature was beta-amyloid plaque accumulation in the brain, but, to date, costly drugs designed to reduce beta-amyloid levels offer only marginal clinical benefit and pose significant risk of harm. Thus, there is strong interest in finding alternative AD-modifying interventions, and, despite controversy, aducanumab—an antibody—recently received approval by the US Food and Drug Administration. This article considers how ethical issues in the care of patients with AD could influence, for better or worse, clinicians' judgment about whether and when to recommend aducanumab.

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Aducanumab Controversy

Dementia (also known as major neurocognitive disorder in the fifth edition, text revision of the *Diagnostic and Statistical Manual of Mental Disorders*¹) remains an incurable illness, with Alzheimer's disease (AD) accounting for 60% to 80% of dementia cases.² AD entails heavy caregiver and financial burden, as it causes progressive deterioration and eventual death of the patients suffering from it. This impact, magnified by an ageing population, has vastly accelerated efforts to effectively treat this disorder. Until recently, there were only 5 US Food and Drug Administration (FDA)-approved treatments for neurocognitive symptoms of AD³; however, there are no agents that alter the disease course of AD.

Two clinical trials conducted by the manufacturer of aducanumab showed reduction of brain beta-amyloid (A β) levels in patients with early-stage AD.⁴ In 2021, aducanumab was granted accelerated approval by the FDA as the first potentially disease-modifying treatment for AD and the first FDA-approved AD therapy since memantine in 2003.⁵ Although researchers believe that A β clearance by aducanumab is a rational mechanism to slow cognitive decline in AD, there has been significant controversy surrounding the FDA's approval of this drug. First, there is no correlation between the reduction of A β

plaques and clinical improvements in trials to date.^{6,7,8,9} Additionally, the price of aducanumab was initially 56 000 USD per person annually.¹⁰ In January of 2022, the price was cut to 28 200 USD per year for a person of average body weight (74 kg)¹¹; however, the full cost extends beyond the drug itself, as patients will require close monitoring with brain scans.¹¹ Although Medicare announced a national coverage determination process,¹² there are likely to be substantial out-of-pocket costs for many patients. Many have commented on the FDA's approval of aducanumab,^{6,10,13,14,15,16} and a postapproval confirmatory trial will not be completed until 2030.¹⁷ Meanwhile, the **toll of dementia** on individuals and families continues to grow.¹⁸ In this article, we canvass ethical considerations that can arise in the care of patients with AD and apply them to the case of aducanumab.

Quality of Life

Given the absence of disease-modifying treatments for AD and AD being an incurable illness with deterioration that ends in death, clinicians' focus appropriately turns to quality of life. In aiming to maintain or enhance the patient's quality of life, clinicians must uphold the ethical principles of beneficence, nonmaleficence, and respect for patients' autonomy—and, in the case of neurocognitive disorders, protection of those with diminished autonomy.¹⁹ One approach to supporting quality of life consists in helping patients obtain as much freedom from their disease as possible, while maximizing their functioning and engagement in their world.²⁰ At its core, maximizing quality of life represents a clinician's obligation of beneficence. In cases of incurable illness, beneficence must be weighed against the autonomy of the patient (and family) to decline or stop treatments that may have become onerous (eg, cholinesterase inhibitors might cause side effects that outweigh their benefits²¹).

With any treatment in cases of incurable illness, important considerations pertaining to quality of life include the following¹⁹: Are we, as clinicians, offering the patient a net benefit? What are the prospects, with or without treatment? It is important to understand that in seeking to “do no harm” and acting in the patient's best interest, we are not ethically obligated to keep the patient with incurable or chronic illness from being affected by it—that is often impossible. Jennings et al eloquently noted that the primary obligation is rather “to assist the person in keeping the transformative power of illness under control, to integrate new subjective interests (wants) and new objective interests (needs) into a coherent and satisfying life.”²² This aim will look different depending on the disease and the individual in question, making it crucial to understand the individual and how the individual experiences the disease throughout its course.

In the case of aducanumab, the lack of clinical improvements in trials to date and risk of side effects such as brain edema,^{4,6} combined with the considerable cost, does not suggest a population-level justification on the basis of quality-of-life arguments for widespread use of this medication, at least at the present time. In fact, the significant financial burden^{23,24} could reduce quality of life by creating financial stress or limiting a family's ability to provide other necessities, such as food, shelter, amenities, or ancillary care. One could argue that lack of any other disease-impacting treatment justifies the use of a medication with limited proof of efficacy. A counterargument, however, would be that lack of alternatives does not justify the application of a questionable or ineffective treatment. Put another way, prescription of an ineffective medication just for the sake of having an intervention is a very expensive placebo, and in general, placebo use is not regarded as ethical standard of care.

Resource Allocation

Resource allocation is a significant concern in the care of patients with AD. The financial burden of dementia care is high, and few families are able to handle these costs entirely out of pocket. This burden (ie, unreimbursed care) is spread among patients, their families, insurance providers, federal and state programs, and health care facilities. In the case of aducanumab, an ethical tension exists between beneficence (providing a potentially useful treatment) and justice (fair distribution of a limited resource). Jennings et al have noted: “Justice does not require that individuals should receive any and all health care they might conceivably want. Equitable access does not mean unlimited access, either for acute or chronic care.”²²

In decisions about allocation of a high-cost medication such as aducanumab, it is important to note who is paying for the treatment. When individuals pay for their own treatment, they allocate their own resources according to their own values and objectives. However, when tax payers or third parties fund treatments, important ethical questions about resource allocation arise.²⁵ The decision to give financial and research priority to a particular condition requires careful consideration of the effectiveness of alternative interventions, the cost of treatment, and the impact of that condition on the physical and mental health of patients, families, and caregivers. As mentioned, the cost of aducanumab was initially 56 000 USD per person annually, a price tag that was estimated to exceed Medicare spending in 2019 on all other infused drugs combined and to entail cumbersome out-of-pocket payments for patients.^{23,24} Whittington and colleagues noted that aducanumab would need to be priced at a discount of 85% to 95% from the launch price of 56 000 USD to meet commonly cited value thresholds.²³

Public Trust

An impartial and scientifically rigorous review process promotes **public confidence and trust** in the medication approval process, which is highly important—and not just for aducanumab. Both clinicians and consumers might not have the time—or the expertise in some cases—to review the efficacy and safety data themselves. If an approval process is abbreviated for any single medication, the public and clinicians might not only view that medication with skepticism, but also lose confidence in review processes in general, compromising introduction of other treatments.

The approval of aducanumab proceeded after the FDA’s independent advisory committee recommended against it.^{6,12,26} Here, an argument could be made that lack of any other available treatments could justify an individualized and accelerated review. However, few other medications are allowed to continue undergoing review with the same level of evidence of clinical efficacy and high cost as aducanumab—and against the recommendations of the advisory committee, as did aducanumab. Maintaining transparency and uniformity in the process by which medications are reviewed and approved is pivotal to and safeguards the trust of patients and clinicians. Since the FDA’s approval of aducanumab, the US House of Representatives and the US Department of Health and Human Services have opened investigations into the aducanumab approval process and accelerated approvals, respectively.^{17,27} In December 2022, results of a congressional investigation into aducanumab’s regulatory review and approval, pricing, and marketing were published.²⁸ This report noted that the FDA’s review and approval of aducanumab consisted of atypical procedures and that the drug manufacturer had aggressive launch plans despite concerns about the drug’s efficacy, safety, and affordability.²⁸ Controversy surrounding aducanumab—a medication

that might have received approval that would not have been granted for other medications—seems to have impaired trust in the review process.

Conclusion

Clinicians are bound to face ethical challenges in the treatment of AD, given the scope and severity of the disease, with the introduction of novel treatments making the discussion even more complex. Adding further complexity, the approval of aducanumab by the FDA represented an unprecedented move on the part of the agency. Aducanumab was approved against the recommendations of the advisory committee premised on its ability to clear beta-amyloid from the brain rather than on evidence of clinical benefit to the patient—a requirement for all previously approved AD therapies. We hold that, in approaching the care of patients in AD, clinicians are on their most sound ethical footing when quality of life is considered a primary imperative.

There is little to support the notion that this medication will directly improve quality of life for the majority of patients or for their families. In the absence of proven quality-of-life benefits of aducanumab, combined with its considerable financial burden and unusual FDA approval process, we find it difficult to justify the widespread use of aducanumab for the average AD patient at the present time. This calculus might change with additional data, changes in cost-benefit ratio, or other factors.

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