

The VA Goes Its Own Way on Aducanumab

Now, in entering the path there are many roads. To summarize them, they reduce to two types. The first is entrance by principle and the second entrance by practice.

Bodhidharma



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In the Veterans Health Administration (VHA), the current prevalence of veterans with dementia is estimated to be about 10%.¹ A 2013 report from the VHA Office of Policy and Planning projected a 22% increase in patients with dementia between 2020 and 2033. That increase amounts to between 276,000 and 335,000 additional veterans enrolled in the US Department of Veterans Affairs (VA) health care.² Of course, these alarming statistics can in no way begin to convey the devastating biopsychosocial impact of Alzheimer disease and other dementias on veterans and their families. In many cases, veterans' service to their country resulted in injuries and illnesses that increased the risk that they would develop dementia, such as traumatic brain injuries and post-traumatic stress disorder.³

Confronted with these concerning statistics, why didn't VA Pharmacy Benefits Management (PBM) follow the US Food and Drug Administration (FDA) approval of aducanumab-avwa for patients with dementia? Instead, PBM issued a monograph in July 2021 that recommended against providing aducanumab-avwa to patients with Alzheimer dementia (mild or otherwise) or mild cognitive impairment, "given the lack of evidence of a robust and meaningful clinical benefit and the known safety signal."⁴

In this editorial, I examine the reasons for the PBM recommendation, explain how the VA denial of approval for this new drug for dementia contravened that of the FDA and the ethical implications of this decision for veterans with dementia and the health care professionals (HCPs) who treat them.

The VA PBM national drug monographs are scientific reviews of clinical data supporting the potential inclusion of new medications in the VHA formulary. Aducanumab-avwa is a human monoclonal antibody. Its mechanism of action is to

stimulate clearance of β -amyloid plaques from the brains of patients with Alzheimer disease. β -amyloid is a protein byproduct of amyloid precursor protein. Abnormal levels of β -amyloid build up in the brain of a patient with Alzheimer disease, forming clumps that disrupt neuronal connections that enable information transmission and other functions contributing to the death of brain cells.⁵

The FDA approved aducanumab on June 7, 2021, through the accelerated approval pathway.⁶ Drugs approved through the regular pathway must show a clinical benefit. Because detecting and demonstrating clinical benefit through research can be a lengthy process, in 1992 the FDA initiated the accelerated approval pathway. This alternative regulatory option permits the agency to approve a drug that "filled an unmet medical need" for a serious or life-threatening condition based on a surrogate endpoint.⁷ Examples of such endpoints are laboratory values, imaging evidence, physical signs, or other objective findings that are believed to predict a clinical benefit. In 2012, the FDA Safety Innovations Act expanded the basis for approval to an intermediate clinical endpoint: a measure of a therapeutic effect that demonstrates a "reasonable likelihood" of predicting clinical benefit.⁷

The FDA, unlike the PBM, found that aducanumab "provided a meaningful therapeutic advantage over existing treatments." The FDA underscored that unlike other medications currently available to treat Alzheimer dementias that target symptoms, aducanumab acts on the underlying neurophysiology and neuropathology of the disease based on the decrease in β -amyloid plaques in participants in 2 large clinical trials. The FDA approved the drug for the treatment of patients with either mild cognitive impairment or in the mild state of Alzheimer dementia.

From the time of its announcement, the FDA decision to approve the drug was controversial and criticized in both professional articles and the news media. A particular poignant charge by Largent and Lynch was that the FDA had exploited the desperation of vulnerable patients with dementia and their families willing to try medications with unclear value and uncertain risk precisely because they believed they had no other viable options.⁸ Critics charged that the FDA took the unusual step of overruling the recommendations of a council of its senior advisors, claiming that there was insufficient evidence for approval; that there was a potential conflict of interest between the agency and the pharmaceutical industry; and that the FDA inappropriately used the accelerated approval pathway.⁹ In August 2021, in response to these critiques, the Office of the Inspector General announced that it would review the process the agency used in approving the drug.¹⁰ Nor was the VA alone in its refusal: The Centers for Medicare and Medicaid (CMS) has proposed to cover the drug for its beneficiaries enrolled in CMS-endorsed clinical trials with the caveat that the drug's manufacturer, Biogen, must continue to conduct studies on the safety and effectiveness of the drug.¹¹

Why did VHA come to a different scientific conclusion than that of the FDA? In reviewing the data from the 2 major studies, PBM did not find that this surrogate endpoint of reduction in β -amyloid plaques was a valid measure of a meaningful clinical benefit. Further, this lack of valid therapeutic change could not outweigh the risks of the amyloid-related imaging abnormalities (ARIA) in research participants. ARIA include cerebral vasogenic edema, effusions in sulci, microhemorrhages in the brain, and/or localized superficial siderosis. These findings are thought to be the result of the antibody binding to β -amyloid deposits that in turn increase cerebrovascular permeability.⁵

Thus, in not approving aducanumab, PBM and VHA leadership acted on the core bioethical principles of beneficence and nonmaleficence to prevent harms that pro-

portionally outweighed benefits. Another ethical consideration for the VHA was that of distributive justice given the expense of the medication and the VHA obligation to be responsible stewards of public resources. At the time of the VHA decision, a year's worth of aducanumab cost about \$56,000: In December 2021, the manufacturer announced a dramatic decrease in the drug's price.¹² Although it may seem that fairness requires the VHA to provide any possible treatment for veterans whose cognitive impairment is in part an adverse effect of their time in uniform, a stronger counter argument is that the same high safety and scientific standard should be used for the approval of medications for patients with dementia as for any other disorder.

Among VHA HCPs and their patients with new and early diagnosed mild cognitive impairment or mild dementia, what is lacking in PBM's clinical ethics analysis is the important principle of autonomy. PBM did carve out a space for the use of the drug in "highly selected patients by experts and centers that have the necessary diagnostic and management expertise."⁵ The series of safety standards that must be met along with monitoring for the drug to be prescribed is PBM's effort to obtain an equilibrium between preventing harm while respecting professional judgment and patient choice. PBM and VHA will reconsider its criteria if research shows improved effectiveness and safety. As with most debated decisions, for some patients and HCPs that balancing act may not have gone far enough, yet many believe that VHA for now is on the right side of the controversy.

Disclaimer

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