What You Should Know About Aducanumab and Other Dementia Drugs

By Randy Dotinga

By the time many patients with severe dementia require long-term nursing care, medications such as cholinesterase inhibitors may be safely deprescribed to minimize the potential adverse events that outweigh the limited long-term benefits.

Now a controversial new drug to treat Alzheimer's disease is garnering a tremendous amount of attention and raising big questions for patients and families: Is this a game changer? Should people with dementia be prescribed aducanumab (Aduhelm), a monoclonal antibody that targets the buildup of beta amyloid in the brain?

AMDA – The Society for Post-Acute and Long-Term Care Medicine, other medical organizations, and many experts are uniting behind a simple message: there are insufficient data to support prescribing aducanumab to older adults living with dementia despite its recent approval by the U.S. Food and Drug Administration. (Read the Society's position statement on aducanumab: *J Am Med Dir Assoc* 2021;22:1777, https://bit.ly/3uH94PR.) Medicare has weighed in too, announcing that it won't cover the drug outside of clinical trials, a decision that will greatly limit its use.

Still, medical professionals are likely to get questions from patients, families, and colleagues about the current state of dementia treatment and whether aducanumab is an advance worth considering.

Existing Treatments for Dementia

The first thing to know is that existing dementia drugs, the ones that have been available for years, have limited effectiveness at best. These medications include the cholinesterase inhibitors — donepezil (Aricept), rivastigmine (Exelon), and galantamine (Razadyne) — and an NMDA (N-methyl-D-aspartate) receptor antagonist, memantine (Namenda). Each works by boosting or regulating the levels of chemical messengers (acetylcholine for cholinesterase inhibitors or glutamate for memantine) that are involved in learning, memory, and judgment (Mayo Clinic Staff, "Dementia: Diagnosis and Treatment," Mayo Clinic, updated July 2021, https://mayocl.in/3Fc7hpJ).

"The way to think about [cholinesterase inhibitors] is they slow down the decline from dementia by about three months compared to people who don't take them," said Lea C. Watson, MD, MPH, a geriatric psychiatrist in Denver and co-chair of the Society's Behavioral & Mental Health Advisory Council, in an interview with *Caring*. "They don't make things better." Well-meaning outpatient clinicians in the community may prescribe the drugs thinking they can keep patients on them indefinitely, she said, but "they're not benign." Their significant side effects include insomnia, diarrhea, weight loss, and arrhythmias.

All these dementia drugs are candidates for deprescribing in the nursing home setting, where severe cognitive decline is common. "When people come to live in a nursing home, it's usually a sign that dementia has progressed and the medications would not be helpful," Dr. Watson said.

FDA Approves Aducanumab and Faces Immediate Outrage

Aducanumab (Aduhelm), which is made by the pharmaceutical company Biogen, entered the picture in June 2021 when the FDA granted the drug accelerated approval as a treatment for Alzheimer's disease (FDA News Release, June 7, 2021, https://bit.ly/37amxqB). Before this decision, the FDA's Peripheral and Central Nervous System Drugs Advisory Committee had overwhelmingly voted against recommending approval (*Nasdaq*, Nov. 6. 2020, https://bit.ly/3LHxG0W).

The FDA's decision on the approval of aducanumab has been widely criticized. Concerns include the effectiveness of the drug, its potential side effects, the scientific merit of the underlying studies, and the controversial FDA approval process itself. As the authors of a commentary in *Nature Reviews Neurology* (2021;17:715–722) wrote, "a broader concern is that the FDA has inadvertently been co-opted to serve the interests of special groups over the general interest of the public," in part because "legislative changes intended to speed up the approval process ... have potentially increased the FDA's reliance on industry funding, undermined its regulatory independence and weakened regulatory standards." These authors and others have further questioned the role of patient groups like the Alzheimer's Association, who were also recipients of Biogen funds, in lobbying for the approval of the drug.

Mark H. Ebell, MD, MS, a family physician and professor of epidemiology at the University of Georgia, said in an interview that aducanumab "was approved based on its ability to change how scans look, and that it has not been shown to improve memory or function." And, he added, it has "potentially serious side effects," including vasogenic edema

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medication) were typically a result of flawed systems.

If a system is flawed to the point where it permits medication errors, is it fair or just to punish a single health care practitioner? Why not fix the system and incorporate fail-safe measures and redundancies learned from human factors engineering?

The medical community could learn from the Federal Aviation Administration's Aviation Safety Reporting System (ASRS), which is a confidential and *nonpunitive* voluntary reporting system of adverse occurrences and near misses. Not having actionable data because a practitioner chose not to disclose a medication error due to a fear of loss of a license, a job, and possible criminal conviction is a missed opportunity to correct a system in need of repair.

Adverse Effects

High-profile criminal charges and convictions likely have an adverse effect on practitioners and health care facilities making voluntary disclosures when adverse events, especially patient deaths, occur.

According to an internationally recognized pioneer in the area of medication safety, Michael Cohen, RPh, MS, ScD (hon), president emeritus and founder of the Institute for Safe Medication Practices (ISMP), "Information about the cause and nature of medication errors is important. Yet even when no patient harm occurs after a medication error, health care practitioners won't want to risk disciplinary action for their involvement, and may just choose to hide an incident under the rug." Consequently, valuable information is forever lost that could prevent future adverse events.

Dr. Cohen's sentiments are echoed by the American Nurses Association (ANA) in a statement responding to Vaught's criminal conviction: "ANA believes that the criminalization of medical errors could have a chilling effect on reporting and process improvement" (*Nursing World*, Mar. 23, 2022, https://bit.ly/3KeHJJi).

One of the witnesses at Vaught's trial, Ramona Smith, an investigator with the Tennessee Bureau of Investigation, testified that "Vanderbilt Medical Center carried a heavy burden of responsibility in this matter." Yet interestingly no charges were brought against Vanderbilt even though it failed to report the fatal medication error to the Tennessee Department of Health and the Centers for Medicare & Medicaid Services. Additionally, a physician at Vanderbilt listed the cause of death as "natural." (Vanderbilt settled with the former patient's family for an undisclosed amount.)

Past Prosecutions

Unfortunately, Ms. Vaught's case is not the first time that medication errors have been treated as criminal homicides and will likely not be the last. Several years ago an overly aggressive district attorney in Denver, CO, charged three nurses with criminally negligent homicide after a fatal dose of penicillin was administered to a newborn who immediately went into cardiac arrest and died.

On behalf of ISMP, which is considered one of the leading organizations regarding medication safety, Dr. Cohen provided expert testimony for one of the nurses, who pled not guilty. Dr. Cohen analyzed all the relevant medical information and found that there were myriad errors in a broken system that allowed for the lethal dose of penicillin: the obstetrician who ordered the drug was covering for another obstetrician; the covering obstetrician did not need to prescribe penicillin for the pregnant mom (who had had a sexually transmitted infection more than 10 years prior); the pharmacy made a 10-fold error in dispensing; and a drug reference book contained inaccurate information regarding whether the medication could be given intravenously instead of intramuscularly.

These were only some of the system's errors that ISMP identified. Dr. Cohen noted that "by reconstructing how the system failures contributed to the tragic outcome, the jury was able to understand how the flawed system allowed the nurse to make such an error." The nurse in this case was found not guilty, but criminal conviction is clearly not a path any practitioner wants to travel down.

Treating Unintentional Error

The question remains: is criminal prosecution the correct approach to an unintentional error? If we have learned anything about medication errors, it is that they are system problems.

This prompts the question: is it fair to criminally scapegoat a single health care practitioner? There are important societal goals, such as making the medication delivery system safer. Perhaps, using the legal system to punish those involved with medication errors is not the most enlightened approach to enhance safety.

In this instance, the legal profession can learn from the Hippocratic Oath: *Primum non nocere* (First, do no harm).

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and microhemorrhages, "and requires regular brain scans to monitor for these problems." (See also: "A Year in Review" on page 10 of this issue of *Caring*).

In September 2021, the Society's position statement on aducanumab said, "We believe that the lack of evidence of benefit, along with the significant potential for dangerous side effects (>30% of study participants had brain swelling or bleeding), high medication delivery cost (initial pricing for the drug alone is projected at $56,000.00/y, and it requires intravenous infusion), and potential for providing false hope is likely to have extraordinarily negative consequences for the 6 million people and their caregivers living with dementia in this country."

The statement adds that "AMDA also acknowledges that our PALTC workforce bears a disproportionate burden because of the high concentration of people living with dementia in long-term care. We must answer to families and caregivers who are desperate to try 'anything that might help'; however, it is our responsibility to resist the urge to prescribe a potentially dangerous and ineffective medication that is untested in our population, even if it has FDA approval" (1777).

Dr. Watson, the lead author of the statement, said that based on the process and the evidence, the drug should never have been approved. It's especially important for medical professionals to understand that it hasn't been tested on anyone in a nursing home, she said.

Focus on Emotions First Before Educating Loved Ones

Long-term care professionals may hear from family members who are curious about whether aducanumab may be appropriate for their loved ones. In an interview, Paige Hector, LMSW, a professional social worker, recommended working to understand the emotions of family members before turning to education mode.

"Perhaps they're looking for reassurance or simply to feel heard," she said. "Consider how you can respond appropriately in a way that eases their pain." For example, you could "acknowledge how much they love their mother, how desperately they'd like this disease to go away, and how this is super hard."

If a family member asks about aducanumab, it can be helpful to note that it's only approved for people who are in the mild stages of Alzheimer's disease, said Lauren Hunt, PhD, RN, FNP, a geriatric nursing care specialist and assistant professor at the University of California at San Francisco. "It is not indicated for people with moderate to severe dementia, which accounts for most people in the nursing home setting," she said.

You may also wish to note the drug's serious side effects, such as brain bleeds, and point out that "many behavioral symptoms and problems for people with moderate to severe dementia in the nursing home can be managed with nonpharmacological interventions," Dr. Hunt said.

Indeed, nonpharmaceutical strategies such as individualized person-centered care, private rooms, and household models of care such as the Green House model have been shown to improve the quality of life for people living with dementia and their caregivers, Dr. Watson said. (Readers can visit www.nursinghometoolkit.com for more on nonpharmacological strategies.)

What's next on the medical front in dementia and Alzheimer's disease? According to the Mayo Clinic, drugs that target beta amyloid (like aducanumab) and tau tangles are in clinical trials, and researchers are exploring whether anti-inflammation treatments are helpful ("Alzheimer's Treatments: What's on the Horizon?" Mayo Clinic, June 30, 2021, https://mayocl.in/3LHgqZE). Other approaches are being studied, too.

In the big picture, however, "there are things that can make the process of having dementia better, but there are no imminent cures for people already living with dementia," Dr. Watson said. "We need to change the focus from cure to care."

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