COMMENTARY

THE AMERICAN JOURNAL of MEDICINE®

The Current State of Pharma and the FDA: Approval of a Dementia Drug as a Case in Point

We are grateful to the scientists who developed the coronavirus disease 2019 (COVID-19) vaccines and to the companies that brought them to market. Such gratitude does not obviate the adverse developments in the pharmaceutical industry-Federal Drug Administration (FDA) relationship that impact US health care, its patients, and burgeoning health care costs. The latest and most flagrant example is the approval of aducanumab in the treatment of Alzheimer's disease (AD) by the FDA, despite the advice of its own nervous system drug advisory panel *against* approval: 10 no, 0 yes, and 1 abstention.[1] Moreover, 3 members of the panel, all experts in the field, have resigned from the panel, citing this egregious decision and a process that can readily ignore their advice even when unanimous.

Furthermore, an independent scholarly think tank, the Institute for Clinical and Economic Review, also concluded that the drug's risks, including brain microhemorrhages, outweigh its questionable intermediate endpoint benefit.[2] Because its clinical benefit remains in doubt, it may only add cost to the health care system.

The lack of efficacy and the serious nature of side effects did little to deter the decision-making when the world of commerce, financial interests, and consumerism predominate over healthcare ethics and scientific objectivity. One needs to consider why this is so.

First, the theory behind development of this drug is simply wrong or merely outdated. Aducanumab is the latest in a generation of monoclonal antibodies directed against β-amyloid. Its proposed therapeutic efficacy is based on an archaic understanding of the pathogenesis of AD, one that has amyloid as the central causative factor. Although β-amyloid certainly accompanies this disease, the evidence that it is causative has been receding in the rearview window as neuroscience research has unearthed a complex web of multiorgan dysfunction in the aging body accounting for it.[3] Moreover, β-amyloid has significant antimicrobial activity,[4] a fact that goes with the rising importance of immunological dysfunction termed "inflammaging" and chronic low-grade infection in the aging human, leading to dementia.[5] So, the key brain components in AD are not the amyloid deposits but an activated "angry" microglial cell. Instead, hyperphosphorylated tau protein accumulates, lipid and protein peroxidation, metal toxicity, gut microbiome dysbiosis, impaired mitochondrial function, hormonal disruption, chronic infection, and subtle liver dysfunction all contribute to the development of AD.

So why the persistent pursuit of this dead-end in AD clinical research? Because a pharmaceutical company can charge a great deal for a monoclonal antibody, and company executives and stockholders can profit mightily; so why change course? With the way the FDA let the opioid manufacturers have their way, maybe yet another questionable drug may get through. The companies and their lobbyists have substantial influence within the DC Beltway, so this situation is unlikely to change in the future.

Ironically, there is accumulating evidence from neuroscience and case-control studies that much can be done to prevent AD and possibly reverse early stages of the disorder that is cost-effective and readily available.[6] These include vigorous exercise with sweating; low inflammatory diets like the Mediterranean diet or the keto diet;[7] use of spices including turmeric, rosemary, and oregano; the regular consumption of green tea, blueberries, and extra virgin olive oil;[8] stress reduction, including meditation; and much more. But these therapeutic strategies are not going to be evaluated in a manner that would garnish a practice guideline because no institution will spend the hundreds of millions of dollars for such a trial. Furthermore, these self-care strategies are harder to evaluate than a single drug is, given human individuality and variability.

Moreover, in this epoch, many institutional review boards (IRBs) that approve research studies are likely to be a for-profit company (in approximately 70% of clinical research studies[9]). Thus, with profitability so front and center even in the review processes of research, you can expect

Funding: None.

Conflicts of Interest: none.

Authorship: The author is solely responsible for the content of this manuscript.

Requests for reprints should be addressed to Arnold R. Eiser, Adjunct Senior Fellow, Leonard Davis Institute, Adjunct Fellow, Center for Public Health Initiatives, Perelman School of Medicine, University of Pennsylvania, 3641 Locust Walk # 210, Philadelphia, PA, 19104.

E-mail address: aeiser09@gmail.com

0002-9343/© 2021 Elsevier Inc. All rights reserved.
https://doi.org/10.1016/j.amjmed.2021.06.014

burgeoning health care costs with little substantive benefits with notable exceptions like the COVID-19 vaccines.

Isn't it time that medical societies and other professional organizations demand an end to the coziness between Pharma and the FDA? If you think so, ask your medical society or professional organization to take a strong stand on this. We need a wide swath of them to articulate the urgent concern that the status quo is unacceptable and demand change. If physicians and other clinicians do not demand change, nothing will happen.

Don't wait for the politicians to act because they aren't going to do so. It is the patients who primarily suffer from the lack of proper oversight of this powerful industry as questionable drugs reach the marketplace. But clinicians also suffer when placed in the untenable situation such approvals create.

So, thank you, Biogen, for pushing your drug across the finish line. Perhaps, you have accomplished the nearly impossible. No, I don't mean stopping dementia in its tracks. I am referring to removing the blinders from our postmodern eyes so acclimated to moral relativism and revealing what is really going on in much of today's pharmaceutical industry-FDA nexus.

Change may be simpler than it appears. Why not have the FDA advisory panel's decision be decisive? That one change would expedite an improved drug-approval process and remove the economic and political pressures from the decision to which FDA executives are currently subjected.

Time to shift the power equation away from the corporate and FDA executives and back to the medical scientists with expertise and a measure of objectivity in their respective subject. Time to relocate our moral compass, isn't it?

Arnold R. Eiser, MD
Adjunct Senior Fellow, Leonard Davis Institute, Adjunct Fellow, Center for Public Health Initiatives, Perelman School of Medicine, University of Pennsylvania, Philadelphia

References

1. Terry M. Fallout continues as third FDA panel member resigns over Aduhelm approval. Available at: https://www.biospace.com/article/3rd-fda-alzheimer-s-advisory-panel-member-resigns-over-biogen-approval/. Accessed June 17, 2021.
2. Lin GA, Whittington MD, Synnott PG, et al. Aducanumab for Alzheimer's disease: effectiveness and value; Draft Evidence Report. Institute for Clinical and Economic Review. Available at: https://icer.org/assessment/alzheimersdisease-2021/. Accessed June 17, 2021.
3. Eiser AR, Fulop T. Extra-cranial factors in the development of Alzheimer's disease. *Brain Res* 2020;748:147076.
4. Li F, Hearn M, Bennett LE. The role of microbial infection in the pathogenesis of Alzheimer's disease and the opportunity for protection by anti-microbial peptides. *Crit Rev Microbiol* 2021;47(2):240–53.
5. Gritsenko A, Green JP, Brough D, Lopez-Castejon G. Mechanisms of NLRP3 priming in inflammaging and age-related diseases. *Cytokine Growth Factor Rev* 2020;55:15–25.
6. Eiser AR. Preserving Brain Health in a Toxic Age: New Insights from Neuroscience, Integrative Medicine, and Public Health. Lanham, MD: Rowman & Littlefield; 2021.
7. Cunnane SC, Courchesne-Loyer A, Vandenberghe C, et al. Can ketones help rescue brain fuel supply in later life? Implications for cognitive health during aging and the treatment of Alzheimer's disease. *Front Mol Neurosci* 2016;9:53.
8. D'Angelo S. Current evidence on the effect of dietary polyphenols intake on brain health. *Curr Nutr Food Sci* 2020;16(8):1170–82.
9. Kaplan S. In clinical trials, for-profit review boards are taking over for hospitals. Should they? Available at: https://www.statnews.com/2016/07/06/institutional-review-boards-commercial-irbs/. Accessed June 17, 2021.