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Editorial

Consequences of the FDA Decision on Aducanumab for Patient Care and Research

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The recent accelerated approval of Aducanumab has been the most mixed-consequence and historical decision that has taken place in the public health arena during my professional career. When I search for earlier comparisons of similar moment, the National Cancer Act of 1971 comes to mind, based upon what I have learned about it from Siddhartha Muckherjee's "biography of cancer (1)." That, too, evidently involved passionate scientists with widely differing opinions, politics, and the loud voices of influential advocacy groups. There was a large outcry protesting the interference of politics and social concerns into the integrity of the scientific process. The approval of the National Cancer Act enabled many diverse efforts to treat a host of cancers, often treatments that would have been considered too high risk before the Act, resulting in some treatments that devastated patients, and some treatments and innovative approaches (e.g. combinations) that eventually worked.

More recently, in 1987, the approval of Azidothymidine (AZT) as a treatment for HIV/AIDS also shares similarities with the approval of Aducanumab (2). There was a global crisis due to increasing numbers of patients affected by the disease, an unclear scientific understanding of the cause of the disease, and no treatments other than drugs to treat secondary infections. The Food and Drug Administration had to decide about approval quickly, reviewing an application that was based upon a small trial with methodological flaws; a trial that was stopped early (in that case because of efficacy); and a reported treatment effect that many questioned as being not clinically meaningful. Further, the drug was associated with substantial side effects. Many scientists and clinicians denounced the regulatory process, accusing the agency of responding to social forces instead of upholding scientific standards. There were calls to investigate the Agency. Once on the market, the cost of the drug was prohibitive for many infected patients. Many observers have credited the approval of AZT with spurring additional research into the causes and treatments for HIV/AIDS, research which eventually led to dozens of approved drugs, largely based upon combination approaches that would not have been possible without so many mechanisms of action to choose from. Yet the value of AZT itself for the prevention and treatment of HIV/AIDS remains controversial even today.

In our own historic moment, what can we who are involved say about the consequences of the FDA approving Aducanumab? We cannot know the ultimate outcome, or the impact that this decision will have for patients, research and society as a whole in the years to come, but can only share our personal experiences, our worries, and our hopes. In that vein, I speak for myself, and not as a representative of any company or organization with which I am affiliated.

The approval of Aducanumab will likely help some patients to decline more slowly from their Alzheimer's condition than they otherwise would have. This is a huge accomplishment for patients, clinicians, researchers and the army of dedicated company employees who worked for years to achieve this outcome. As far as we know today, the patients most likely to be helped are those similar to the patients included in the EMERGE trial. Yet the inconsistent outcomes in EMERGE compared to those in ENGAGE will temper the enthusiasm of some clinicians for even trying the drug. Often the persistence of a treatment is as much a function of the clinician as it is of the patient. If clinicians have difficulty discerning benefits to patients, which is often the case when an illness is expected to progress despite treatment, it will re-enforce their lack of enthusiasm for treatment.

The Aducanumab prescribing information does not limit the drug's use to this population of individuals who are most likely to benefit. Biogen has added to the label, after the initial approval, that treatment should be initiated in patients with MCI or mild AD, but there is no guidance regarding when to stop treatment and the wide indication statement "for the treatment of AD," remains. Some clinician researchers are attempting to help by making their own recommendations to guide clinical practice (3). Many commentators have reacted against the wide indication, thinking that it goes well beyond the evidence, and exposes patients who may be unable to benefit to unnecessary risks, and the lack of limitations increases the cost to payers. But the wide

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label also facilitates our thinking about AD as a series of neuropathological changes in the brain, reflected by biomarkers, as opposed to waiting for the clinical manifestations to identify the disease. This wider conception of AD could help to reverse some historical and artificial constraints on AD drug development. In most diseases, we do not have to develop drugs for patients one severity segment at a time. We do not, for example, have drugs that are developed and approved specifically for metabolic syndrome, or just for early diabetes, or moderate diabetes or severe diabetes. The time and resources lost by doing drug development in this step-by-step way are enormous. I have often thought that we were painting ourselves into a corner in AD research by studying AD drugs in one population segment at a time, beginning with the cholinesterase inhibitors (4-7). We did it, in part, because of the nihilism associated with the hypothesis that one could actually treat AD. Drug developers feared that wide labels would work against approval and reimbursement. The field also pursued this development strategy because of the lack of outcome measures that we were sure could capture a benefit across all of the disease stages. Maybe one consequence of the FDA approval of Aducanumab with a wide label is that we can start to think of AD in a more natural way, on a continuum, and change our expectations for therapies. Perhaps treatments should be expected to benefit more patients, even if the effect varies by stage or severity. Instead of limiting drugs by stage, our efforts to identify predictors of response can accelerate as a way to personalize the treatments and limit wasted resources.

The approval of Aducanumab will likely also cause hardship for some patients. As a practicing clinician in an academic neurology clinic for over 20 years, I accompanied many patients and their families on their journey with AD. Our practice and research setting emphasized follow up of the patient for the duration of their disease, sometimes from the time of detection in our Healthy Aging Program, through years of Mild Cognitive Impairment, to mild, moderate and severe stages of AD (8). Although we offered clinical trials to every eligible patient, the percentage who participated steadily went down over the years, once symptomatic treatments came on the market. Yet some patients participated in multiple clinical studies (with no treatments offered) and clinical trials because they thought that better disease understanding and treatments were needed and wanted to help make that happen. Other patients and their families looked for any and all potential treatments outside of clinical trials, regardless of the cost, and regardless of where they had to go to get the treatment. People in this latter group were not necessarily financially privileged. I saw families who sold their vehicles, or took out a second mortgage on their home, or crowd-sourced from family and friends just to try drugs and treatments that they could get outside of a clinical trial. Sometimes these were marketed drugs for which information in the media suggesting their use for AD, and so they sought off-label use. Or sometimes the drug was already in a clinical trial for AD, but available by prescription for other indications. These off-label uses of drugs for AD were not covered by insurance. Often, families could not raise enough money to continue the treatment for the hypothesized duration that was necessary for a treatment effect. Even knowing this, they would try it anyway for a few doses. So, it is likely that some families will risk serious economic insecurity by trying to keep up with co-pays for Aducanumab, or to pay for it out of pocket. Other patients will be denied access by healthcare systems who have to make difficult decisions about what drugs to cover or not to cover, and these patients and families who cannot get the treatment will suffer emotionally from thinking that there is a potentially effective treatment that they cannot obtain for themselves or their loved one. While the FDA approval of Aducanumab may help some patients, it may cause tremendous hardship for others.

What are the consequences of Aducanumab's approval for research? Proper informed consent requires that patients who are currently in a clinical trial of an AD therapy, or patients considering entering one must be told about all available alternatives, including all approved therapies. Since trials usually involve double-blind periods where there is a chance that the patient will get placebo, some patients will opt for the newly approved drug by prescription instead and drop out of ongoing trials. This could render several years of their own and/ or of a company's investment into an ongoing trial as worthless, if dropout rates are too high to draw conclusions about the treatment under study. If enough patients exit ongoing studies or fail to enroll in new ones that are placebo-controlled, which are still the gold standard for drug development, the development of additional new treatments will stall.

Many trials may be pressured to allow the new drug as a background treatment, despite the questions about efficacy, and to the detriment of the scientific questions being asked in the study. Since the clinical effects of Aducanumab have been variable across studies, it would be difficult when designing trials to predict the rate of change in placebo-treated patients on this background, affecting study power calculations and increasing the cost of trials. A requirement to allow background Aducanumab would circumvent the use of digital twins or other real world control groups, slowing down innovative approaches to drug development. Safety monitoring for trials of new drugs in which background treatment with Aducanumab is allowed would have to factor in drug interactions as well as adverse events attributable to Aducanumab. If sponsors want to reduce variability caused by having some patients on treatment and some not, they can require all participants to be on Aducanumab (an add-on study design as opposed to

allowing the drug as background therapy), but the cost to the sponsor of supplying Aducanumab to participants could be cost-prohibitive. And because of the wide drug label, these considerations regarding background treatment could theoretically apply to all AD trials, from early AD to advanced AD. Finally, the wide label for Aducanumab, even after the qualifiying statement added by Biogen after the approval, still leaves the door open for the drug to be used by prescription for primary and secondary prevention. Trials in these populations are large and long in duration, so that commitments to provide Aducanumab to some or all of the participants in such prevention trials would be impractical. If there is widespread use of Aducanumab in preclinical or very early stages of AD outside of clinical trials, new treatments that might be ideally suited to these stages of the disease may never be developed. Already, the approval of Aducanumab has raised such challenges for ongoing platform studies, such as the Dominantly Inherited AD Network, as there are no data on the dose or safety of Aducanumab for this genetic population, but patients who progress in these trials may expect to receive the treatment.

In conclusion, the FDA approval of Aducanumab is a hand-wringing historical development. People will be helped and hurt, research will be advanced, slowed, and in some cases potentially made impossible. Public confidence in the regulatory process has once again been called into question, and the ability of most people to even understand the risks and benefits of the new drug has been compromised by the complex study results and contested regulatory decision. Change is inevitable, and there can be no progress in science without change. So each person involved in this present-day history-making event is free to decide what he/she would have done differently, or thinks of the drug approval, and most importantly, how they plan to conduct their AD clinical and research efforts, given the news. The hope is that, collectively, we will go on to do better at preventing and treating Alzheimer's disease.

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