Why There Will Be No (Effective) Drug Therapy For Alzheimer's

Often misdiagnosed. (Almost) always misunderstood. Alzheimer research is plagued with both myopic thinking and a vexing natural history.

July 6, 2021 By Mike Barr

In the early 1990's seemingly rock-solid evidence from lab mice suggested that Alzheimer's disease was caused by the accumulation in the brain of sticky synapse-destroying plaques made of a piece of a protein called amyloid-beta. Those lab studies indicated that amyloid-beta is formed in the brain by a series of steps, and that either intervening in those steps or destroying amyloid-beta plaques might be an effective way to treat and even prevent Alzheimer's disease.

Since the 1980's most neurobiologists have treated this basic idea, dubbed the "amyloid hypothesis," as dogma. It has won its developers multimillion-dollar prizes, countless accolades, and prestigious academic positions. It has had a huge influence on which Alzheimer's papers get published in top medical journals and what studies get funded.

Just one little hitch: when the drug companies-- Roche, Lilly, Pfizer, and others-- tested the compounds they'd developed based on this presumption, the results ranged from frustrating to bewildering. Human brains simply did not respond to the drugs the way their animal, er... models, did.

It would be one thing if the drugs had failed to do what they had been designed to do: prevent, reduce or clear plaque formation. But that wasn't the issue. In many cases the drugs did a fantastic job. Nature even splashed the dramatic results of Biogen's now super controversial monoclonal on its September 1, 2016 cover: "Before. After." The cure was at hand!

(Although an erratum of sorts was issued a year later.)

The problem was that they, for the most part, did exactly what they were supposed to do-- only that the patients either got no better or, incredibly, in the case of semagacestat, got worse!

It's as if our space rockets kept exploding on the launch pad time after time and we just kept on launching the same rockets from the same pads.

Dr. Amit Roy, a founding partner at Foveal Research who has long viewed amyloid as more bystander than blame bearer, provides even a more flippant interpretation: "The focus on

Alzheimer medicines that target beta-amyloid," he observes wryly, "is like developing drugs for lung cancer that target yellow fingernails."

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And with last week's not only green lighting but accelerated green lighting of aducanumab, the FDA basically showed where it comes down on the amyloid debate, even while trying to have it both ways. One memo included in internal documents on the approval noted that the data from the aducanumab trials was "consistent with the theory," while another said the agency was "not endorsing the hypothesis" or trying to discourage other approaches.

Alberto Espay, professor of neurology at the University of Cincinnati, who freely admits to having been worn down by the group think and politics of this field over the past thirty-odd years, though, begs to differ. "The approval of aducanumab," he writes, "should not be viewed as validation of the amyloid hypothesis." It is only "validation of a brilliant corporate strategy totally disconnected from science."

Acting FDA commissioner Janet Woodcock defended the decision as "very solid," adding further that Congress has encouraged the agency to use its accelerated-approval authority to try to help patients with devastating diseases and few treatments, as occurred with, for example, the first protease inhibitors in the early 1990s, even though the first half dozen or so flopped or, one might argue, consigned early takers to a path of multi-drug resistant virus that greatly limited their chances to benefit from better drugs that came out later on. "My experience from other diseases is that this will lift all boats," she said. In a field that has often been in despair, she added, "there is now hope."

Let them duke it out, but it's hard to see how everyone-- Roche, Lilly, Genentech, others-- is not now going simply to race to filing as quickly as possible. (Just two weeks after the FDA cleared the Biogen drug, Eli Lilly did indeed announce it would seek accelerated approval for its anti-amyloid drug, donanemab, later this year based on a small trial that showed the treatment reduced amyloid plaques.)

Stock analysts are already predicting that, long-term, these three companies, Lilly, Biogen, Roche, will more than likely emerge to share the spoils of this multi-billion dollar market, with donanemab, aducanumab and gantenerumab garnering 50, 30 and 20 percent shares, respectively. And with no one really benefiting, except the drug companies.

And perhaps a few enterprising physicians. Medicare apparently pays 6% of the cost of physician-

administered drugs directly back to the doctor. That's on top of fees for the visit itself and the infusion. For Aduhelm, at $56K, that would come to around $3,360 a patient. Cha-ching, anyone?

Not surprisingly, Biogen has rushed to help interested parties set up infusion sites across the country, with 900 or so said to be already ready to go. And with the FDA granting Aduhelm approval to "all comers" as opposed to only the early stage patients that were enrolled in trials, the potential market is even more attractive: six million or so in the U.S. alone. An estimated 35 million worldwide.

[Update 9 July 2021: two days after this was posted the FDA announced a surprising backtrack to its labeling for Aduhelm, narrowing the indication to only the population studied: "early-stage disease." (And Woodstock herself announced an investigation into her agency's dealing with Biogen that led up to the controversial accelerated licensing.) That does not prohibit physicians, of course though, from using it "off label" for other populations, although it might make insurance reimbursement a bit trickier.]

"I worry about the financial incentive to use this drug even if you don't think it's going to work," commented one health professor who admits to be flummoxed by recent developments.

And yet this would be no different than what already happens today (or has happened historically) in the U.S. with bone marrow transplants for breast cancer, prostate surgeries, hip replacements, knee arthroplasty, gallbladder removal, and others. This is corporate medicine, folks! If you don't believe me, please pick up a copy of Otis Webb Brawley's "How We Do Harm." I read and re-read it in, yes, cliche-ily-- horror, shock, sadness and disbelief-- over and over during the first cold winter months of lockdown. Even created a tabular summary of the unwittingly victimized. Remind me to share later.

To critics of the Aduhelm approval, Lilly's change of heart is Exhibit A that the FDA's decision will spur drug companies to seek quicker approvals based on smaller studies and surrogate endpoints.

But there's another problem too.

Just as tragic as the blinkered adherence to the amyloid hypothesis is mainstream medicine's assumption that Alzheimer's is a single disease (or process). As such, it is typically treated with donepezil (Aricept) and/or memantine (Namenda), and soon, presumably, Aduhelm. Although the chattering classes are already buzzing about the promise and presumed inevitably of, you guessed it, combination therapy!

But neither cholinesterase inhibitors nor glutamate receptor blockers nor anti-amyloid monoclonals get at the underlying cause of Alzheimer's-- or stop it from worsening. And they certainly do not cure it.

What needs to be considered is what is causing the laying down of amyloid (and tau protein production) in the first place. (Dale Bredesen has a very helpful illustration and discussion of this in his book, "The End of Alzheimer's," that I can share in a future post.)

Sit down for this.

Many smart folks, including many smart folks who had spent their entire professional lives dedicated to basic research that might lead to drug development, are increasingly coming around to this view: Alzheimer's is not a disease.

That is, it is not the result of the brain doing something is isn't supposed to do, the way cancer is the result of cells proliferating out of control or heart disease is the result of blood vessels becoming hardened and clogged-- although even these two counter examples could benefit from more robust questioning as to actual "upstream" causes. Alzheimer's arises from an intrinsic and healthy downsizing program for the brain's extensive synaptic network.

What needs to be considered is the cause of aberrant amyloid production in the first place.

Contrary to the current dogma, what is observed upon autopsy or now vie PET scans in patients diagnosed with "Alzheimer's disease" is, these renegade researchers argue, actually a protective response to three general insults: chronic inflammation/infection, sub-optimal nutrition (and other synapse-supporting molecules), and toxic exposure. The brain suffers some injury, infection or other assault and responds by defending itself. The defense mechanism includes producing amyloid.

That's right, the amyloid that has been vilified for decades, the very amyloid that everyone has been trying to get rid of, is part of a protective response. No wonder trying to get rid of it hasn't been very helpful to those with Alzheimer's disease.

Anyone over the age of 40 (without question anyone 50+) stands to benefit by at least considering this admittedly heretical interpretation, especially because the processes of hippocampal atrophy and synaptic dysfunction can take many years, even decades, to get to the point of noticeably cognitive decline.

So, as we used to say with HIV infection, sometimes controversially, "the earlier (you take notice & intervene), the better." Even the king pins at Roche, Lilly and Biogen would likely agree with that.

Future posts in this series will go into more detail about ferreting out and identifying these three main groups of insults-- and how to address them-- as well as early signs, often dismissed or unnoticed, that your brain may already be in trouble.

This and future posts will be kind of a mash-up of reporting by Laurie McGinley and Tara Bahrampour for the Washington Post as well as additional interviews and stats from Financial Times reporters David Crow, Sarah Neville, Hannah Kuchler and Nikou Asgari; from the Buck Institute for Research On Aging's Dale Bredesen, MD and his books; as well as presentations at a recent IFM conference by Harvard's Rudolph Tanzi, PhD, UCSF's Michael Merzenich, PhD and others. In future posts, I will also include links to resources. In the meantime, feel free to reach out to me at my own IFM profile or via my latest kind of St. John's the Divine, forever a work in progress website, The Liberated Brain.
