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Lessons from Alzheimer's Disease (AD) Clinical Trials: Instead of "A-Drug", AD-D prevention to Avert AD

Debomoy K. Lahiri

Department of Psychiatry, Indiana Alzheimer Disease Center, Indiana University School of Medicine, Indianapolis, IN-46202, USA

From our physics classes, we can recall that developing a perpetual motion was a craze of the 19th century. Uncounted would-be inventors found themselves on the verge of discovering a machine that operated at 100% efficiency once started, or even greater efficiency, creating more energy than was used to run it. No matter the failures, these stalwarts soldiered on, convinced that they just had to refine and try one more time and they would have a critical breakthrough that would change the world. Eventually, the search fell to the wayside. We now look on perpetual motion as the product of incomplete understanding of the fundamentals of mechanics and entropy in a real-world system. Is history repeating itself in another field?

In March of this year, all trials were terminated for aducanumab, another (out of at least half a dozen) "promising" antibody-based Alzheimer's disease (AD) therapy [1], Aducanumab, a monoclonal antibody against amyloid-β (Aβ) peptide, had the key difference from some of its predecessors that it was specific against Aβ aggregates and did not recognize Aβ monomers. As is usual in these discontinued trials, it worked well in animal models and managed to get through safety trials.

The ENGAGE and EMERGE trials for aducanumab were well designed, incorporating what was considered the best understanding of AD [1]. Subjects had to meet reasonable screening requirements: Clinical Dementia Rating of 0.5 (very mild), MMSE ≥ 24 (mild MCI or normal), positive PET for Aβ aggregates, and multiple exclusion criteria [1]. The antibody was administered monthly for 18 months. Initial results looked promising, but futility analysis steered Eisai/Biogen to call everything to a halt. Leaving behind the ongoing controversy over the worth of futility analysis, this outcome was a disappointment to the field.

So, what happened? Why did the latest best great hope fizzle? Was it a good fizzle or a bad fizzle? Did we learn anything from the failure? That remains to be seen, depending on how forthcoming the study's owners are with their data. Nevertheless, this latest failure, regardless of what gets published, can be capitalized on, simply because it is a failure.

From sports jargon, some coaches refer to what they call "harder-faster syndrome". This refers to a common response to failure of redoubling efforts in the same direction, merely harder and faster. A more viable tactic is to treat failure as an opportunity to explore alternative approaches. Current approaches share two critical traits: The treatments, regardless of their individual targets, each have a *single* target. They presume that AD stands

on a single protein, and all you have to do is knock over that support to bring the entire disease down ("stilt" approach). Within these approaches, the majority are aggregate-based. Either knock out tau or knock out Aβ, but if you remove an aggregate, everything should just fall into place ("clump-cleanup"). Unfortunately, both approaches are based on what the field is beginning to admit may be an incomplete model of AD.

AD is unlikely to be a single-molecule disorder. Unfortunately, most understanding of AD is based on familial AD (FAD), which is atypical of AD. Known risk (and, by extension, protective) factors vs. the most common form, sporadic AD, do not apply to FAD. Thus, treatments heavily derived from studying animal models based on FAD may be foredoomed. AD is an amyloidopathy *and* a tauopathy *and* a gliosis *and* a metallo-dyshomeostasis, among other features, and the primacy of any of these disease traits over any others has not been established.

Likewise, any of the failed treatments cannot be said to have addressed causes of AD, not due to their failures but because the causes of AD are still unknown. If advanced aggregation of Aβ plaque and tau tangle actually determine AD, why are there people of advanced age who have plaques and tangles but no dementia? The most common response in the field sounds unconvincing: These people still have AD but they do not have dementia. From the perspective of patients and families, dementia is the only thing that matters and they would not care if plaques and tangles multiplied so long as normal living were restored. In a very fundamental way, we still do not know how AD starts or even what it is.

Nevertheless, this does not mean we should surrender. We can still say that in many cases, aggregates are likely to have something to do with progression of AD as a life-altering disease. However, as has been stated more times than can be counted, attacking the aggregate stage may be "too late". Of course, if dealing with the aggregates once they have appeared is "too late", does that mean that the aggregates are just a symptom of AD? In any case, once the molecular hallmarks appear, cellular damage may be irreversible. In addition, how early is early enough? Everyone in an industrial country has been exposed to some risk factor or another for sporadic AD, be it pollution, stress, heavy metals, a poor diet, social alienation, or multiple other selections. Does the "ever earlier" mantra mean that we simply must put everyone over the age of 30 on anti-AD drugs for the rest of their lives? What approaches could work?

AD is complex and heterogeneous. AD can be slow developing and chronic. AD researchers can learn something from metabolic disorders, cardiovascular disorders, and cancers. These three disease fields embrace cocktail and multi-therapy approaches. Why not AD treatment? AD has proved time and again immune to any single-target approach. Rather than focus on traits of advanced diabetes or heart failure, or on stage 4 cancer, research focuses on finding ever-earlier, *accurate* detection and identification of meaningful precursors.

Likewise tackling AD requires multiple steps. Primary preventive steps, such as lifestyle, and supplemental interventions, needs to preceed any disease-modifying interventions, such as anti-amyloid or tau therapy, vaccination, or pioglitazone [2], Such measures should be considered secondary interventions, not primary, much as lifestyle modification is primary to

preventing metabolic and cardiovascular disorders, and drugs are a second line of defense. This also requires our understanding the disease as a transformation rather than a state [3], This opens up exploring other less-studied areas relevant to AD, such as clinical and environmental correlates, and epigenetic factors [2–4]

Treatments could combine symptomatic (such as, cholinergic modulators, anti-cholinesterase, anti-NMDA receptor) along with anti-amyloid and anti-tau drugs. As knowledge improves, the cocktails could be improved. Current one-target-only approaches mean that a substance that might improve upon current treatments *if used in conjunction* are rejected because they do not solve the entire problem on their own. In addition, how often is lifestyle change advised by physicians for early metabolic or cardiovascular signs or symptoms? Quite often! Are physicians taught to do the same regarding AD? Where does prevention currently fit in the family physician's arsenal against averting AD, or is AD simply kicked down the road and never discussed until serious symptoms appear.

The amazing success of antibiotics in the 20th century may have instilled an unfortunate "heroic pharmaceuticals" paradigm, where a magic bullet shoots the magic target and magically eradicates the disease. In general, bacterial infections are far simpler affairs than a sporadic neurodegenerative disease. The ongoing (desperate?) search by a few researchers for an infectious agent behind AD may reflect a desire to have such a simple paradigm. After all, a previously sporadic disorder, gastric ulcers, was found to actually be predominantly due to a single infectious agent. However, such a possibility is remote for AD. The possibility of applying the antibiotic paradigm of one target, one drug, one cure is equally as remote.

Tackling a disorder with the complexity of AD will require us to meet it with an arsenal, not a magic bullet. We need to continue mechanistic studies [5], test potential drug targets, and include lifestyle changes in our clinical responses. In addition, we will need to go beyond obvious symptoms and discover valid precursors that appear early enough to be reversed. The field must consider AD-Ditional preventive approaches instead of "A Drug" to avert AD.

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