Alzheimer’s disease: The right drug, the right time

Lessons from failed clinical trials can improve the development of Alzheimer’s disease–modifying therapies

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Alzheimer’s disease (AD) is an age-associated neurodegenerative disease that is reaching epidemic proportions as a result of the aging of the world’s population. Impressive gains in our understanding of AD pathogenesis have not yet translated into disease-modifying therapies that benefit patients. Is this because the knowledge that guides target identification and, hence, therapeutics, is insufficient? Are current clinical trial designs not optimal? Or are other factors contributing? Here, we highlight the challenges of developing effective AD therapies and discuss how lessons learned from failed trials must be implemented to increase the likelihood of success.

Compelling data support a contemporary version of the amyloid cascade hypothesis (ACH) in the pathogenesis of AD (1) (see the figure). The ACH posits that slow, progressive accumulation of aggregates of the amyloid-β protein (Aβ) in the brain triggers AD by initiating a complex pathological cascade that accelerates tau pathological pathways and leads to neurodegeneration and clinical dementia. Factors such as genetics [for example, apolipoprotein E (APOE) ε4 variant and others], head trauma, lifestyle (for example, exercise, sleep), systemic inflammation, and vascular disease may interact to influence risk or pathologic processes. The ACH provides the rationale for therapeutics designed to (i) alter Aβ aggregate accumulation and the “toxic” actions of these aggregates; (ii) prevent tau accumulation; and (iii) target subsequent cellular dysfunction contributing to the complex downstream neurodegenerative processes that result in symptomatic AD. These diagnostic pathological features of AD can now be assessed by a research classification scheme using imaging- and fluid-based biomarkers in humans, the A/T/N (Aβ/tau/neurodegeneration) diagnostic staging system (2). Further, the ACH provides a framework for aligning different therapeutic interventions with disease stage (3) (see the figure). This framework has not been applied consistently in clinical trials of drugs that target AD. Instead, many drugs were tested at disease stages where there was concern that limited efficacy would be predicted by the ACH, primarily because testing in symptomatic patients was the most feasible route forward. Further, several trials did not define optimal doses or show evidence of sufficient target engagement. To optimize the chances of success, therapies must be tested at a disease stage where they are most likely to show efficacy (i.e., the right time) and do so only when target engagement and an effective dose have been established in early-phase clinical trials (i.e., the right drug). It is also necessary to ensure that preclinical studies supporting advancement of a therapy to human studies are rigorous and reproducible, and to evaluate, to the extent possible, the stage of disease where the therapy is most likely to show efficacy.

Completed disease-modifying AD clinical trials, primarily of drugs that target Aβ, have tested limited aspects of the ACH; many failed in phase 3, the final stage with the potential for U.S. Food and Drug Administration (FDA) approval (see supplementary materials). Only trials with proven target engagement, such as those of solanezumab and verubecestat, truly tested some aspect of the ACH (4, 5). Solanezumab and verubecestat both targeted soluble Aβ, which might slow accumulation in pre-symptomatic stages, but should have limited effects on preexisting Aβ pathology, as predicted from preclinical studies in mouse models (6, 7). In retrospect, such negative results are not surprising—by the time clinical symptoms appear, Aβ aggregates have accumulated over many years and the brain has undergone extensive degeneration.

Can better clinical trials be designed based on the ACH? Assessing disease modification in AD requires multyear cycles of innovation and optimization. Practical, safety, financial, and regulatory considerations have contributed to suboptimal clinical studies. In some studies, a potentially effective drug may have been tested at the wrong disease stage, but in many studies, it has simply been the wrong drug. Although methods are available to assess target engagement and assess efficacy with biomarkers, they have not been applied consistently in early-phase trials. Moreover, evidence for sufficient target engagement was often underemphasized in go-no-go decisions to move therapies into pivotal clinical trials. In several concluded phase 3 studies of AD therapies, ~20% of individuals enrolled with a clinical AD diagnosis did not have AD when biomarker studies were assessed postenrollment (8). Most trials now use Aβ imaging or cerebrospinal fluid–based biomarkers to document AD pathology in participants. This is a critical and ethical step if the therapy is targeting mechanisms underlying AD. Ongoing advances in blood-based AD biomarkers will likely increase efficiency and reduce the costs of cohort selection. Additional progress with biomarkers and more sensitive cognitive assessments that accurately track degeneration and functional decline from the earliest signs of pathology will also improve the chances of success.

AD clinical trials have been powered to detect relatively small changes in rates of cognitive or functional decline (typically, 25 to 30% slowing of decline over 18 months) when AD is symptomatic. These trials require large cohorts, increasing costs and recruitment time. If a statistically significant slowing of decline was achieved, such an effect might be sufficient for FDA approval but may not be clinically meaningful to patients and families. Testing drugs appropriate for disease stage with biomarker-defined participants and using enough patients for larger clinical effect sizes (for example, 40 to 50% slowing of decline over 18 months) could reduce costs and increase predictive power, especially of early-phase trials.

Efforts now focus on testing agents at earlier disease stages where efficacy may be more likely. Secondary prevention trials in asymptomatic individuals who are positive for AD biomarkers and, in some instances, with high genetic risk for AD are testing interventions that target Aβ [for example, the Alzheimer’s Prevention Initiative (9), the A4 study (10), and the Dominantly Inherited Alzheimer Network trials unit (11)]. In contrast to intervention in symptomatic AD, a therapy with modest impact on Aβ could show clinical benefit over time, because pre-symptomatic patients are less affected by tau deposition and structural damage occurring in symptomatic patients. However, not all individuals with positive Aβ biomarkers will develop AD, and they are healthy; these secondary prevention trial drugs require a benign safety profile. Recent guidance from
A framework for selecting the right time for the right drug

The amyloid cascade hypothesis provides a framework for timing interventions, depending on the target and likelihood that a therapy will be successful at a given stage of AD, inferred from cross-sectional autopsy studies and in vivo human biomarker studies (1–3).

Risk factors
- Genetic alterations
- Time (ageing)
- Environmental factors
- Other?

Aβ aggregate accumulation
- Tau and other proteinopathies
- Degenerative changes
- Complex cellular dysfunction
- Symptom onset
- Regional brain organ failure
- Symptom progression
- Widespread brain organ failure

Theoretical time from symptom onset

- > 30 years
- > 20 years
- > 15 years
- > 10 years
- 0 years
- +10 years

Probability of success for AD therapies

Low
- smaller effect size
- associated with failed therapeutic trials

High
- larger effect size
- associated with successful therapeutic trials

Inhibition of Aβ production or aggregation
- Aβ aggregate removal or toxicity neutralization
- Blocking extracellular tau spread
- Tau clearance or blocking tau toxicity
- Correction of cellular dysfunction, including immune therapies
- Neurorestoration
- Symptomatic therapies
- Primary prevention
- Secondary prevention
- Current testing in symptomatic phase

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REFERENCES AND NOTES


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SUPPLEMENTARY MATERIALS

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The FDA (12) suggests that acceptance of biomarker endpoints in clinical trials might be sufficient for drug approval—a considerable change to the requirement for clinical endpoints, which would take far longer. The nature of the biomarker result that might enable FDA approval remains uncertain and, similar to the history of approval of statins for cardiovascular disease, subsequent postmarket (phase 4) studies evaluating clinical efficacy would be required.

Aβ antibodies (aducanumab, BAN2401, gantenerumab, LY3002813) being tested in symptomatic AD patients appear capable of reducing Aβ aggregates, as assessed by Aβ positron emission tomography (PET), in some cases eliminating the Aβ signal (13, 14). Although hints of clinical benefit have emerged from these studies, the effects reported to date are small and potentially influenced by unbalanced cohorts or small group sizes, and will need to be reproduced in phase 3 trials. Autopsy studies will be needed to determine the impact of diminished Aβ PET ligand signal on brain levels of Aβ, tau, and downstream pathology.

The ultimate test of the ACH, and the test most likely to have the greatest health impact, will be in primary prevention studies—where an Aβ-targeting therapy is initiated prior to detectable Aβ accumulation in the brain. No such study has yet been launched, although planning is under way. Such studies will likely require many years to obtain a biomarker readout and even longer to test definitively that an intervention prevents or slows development of AD symptoms. Thus, the therapy needs to be extremely safe and well tolerated.

If Aβ aggregate clearance does not have clinical benefit in phase 3 studies in symptomatic AD, there are concerns that financial considerations may limit enthusiasm for further trials—even though primary and secondary prevention studies are the logical path forward. The expense and cost of trials to show benefit in a slowly progressive disease, coupled with multiple failures, have already resulted in a decline in private sector investments. Loss of investment may accelerate if failures continue.

Patients with mild AD still progress after their PET-Aβ burden is reduced (albeit, possibly, at a slower rate), reinforcing the possibility that downstream changes become independent of Aβ pathology. The point at which this independence emerges is almost certain to be defined by ongoing anti-Aβ trials. Moreover, identification of therapeutic targets beyond Aβ is essential. A limited number of current trials target tau, despite considerable interest and long-standing knowledge of its pathophysiological roles (15). Indeed, the extent of tau aggregation has long been known to have a direct relationship to symptoms; biomarkers, including tau PET imaging, allow it to be assessed in patients. Nevertheless, tau remains a challenging therapeutic target. First-generation tau immunotherapy trials are under way, as are efforts to lower tau levels using modified antisense oligonucleotide and a few small-molecule studies.

Given the unmet medical need and the impact of lifestyle and vascular mechanisms on dementia risk, evaluations of nonpharma
cologic interventions such as exercise, behavioral therapies, and diet are important. Such interventions may have benefit in trials, although the effect size is typically small. On a larger scale, and initiated early enough (midlife), these strategies could lower population risk and have public health benefit.

As interventions are tested to prevent symptom onset, lack of therapeutic success in symptomatic studies may lead to diminishing efforts to develop therapies that benefit those who already suffer from AD. Despite the less certain biology, imperfect animal models, and challenges of treating complex neurodegenerative dysfunction, efforts must continue to identify new therapeutic approaches for the millions of individuals who have AD and the millions who will become symptomatic before an effective prophylactic treatment is identified. Selecting the right drug or drug combination to combat the pathological changes in symptomatic patients is a huge challenge, but one we must take on. We must continue to build a more predictive, translational road map and adhere to the principles of good drug development to ensure that efforts from basic science translated to clinical trial design meet the challenges of treatment and prevention.