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Abstract

The so-called "amyloid cascade hypothesis" provides an elegant explanation of Alzheimer's disease (AD), has motivated the amyloid-lowering therapeutic strategy, and led to the elaboration of a rich experimental and conceptual toolkit for the field to progress. But it might be incorrect. The scientific evidence base supporting the efficacy and safety of current anti-amyloid antibody treatments in AD is weak. Nevertheless, we argue that there is a bias towards the amyloid-lowering therapeutic strategy amongst key opinion leaders in the research and advocacy communities. To demonstrate this, we first focus on the AD lexicon: while any accrual of amyloid on a brain PET scan can now permit diagnosis/definition of AD, lowering positron emission tomography (PET) amyloid is considered disease modification, and treatment-induced side-effects are hidden behind neutral-sounding acronyms: ARIA (amyloid-β (Aβ)-related imaging abnormalities: brain bleeding and swelling) and ARPA (amyloid-β (Aβ) removal-related pseudo-atrophy: brain shrinkage). Second, we underline that drugmakers did not test anti-amyloid antibodies against the best proven interventions and did not adequately inform trial participants of risks, thus violating research ethics of the Declaration of Helsinki on 2 counts. In conclusion, we are critical of over-reliance on the idea that PET amyloid-lowering treatments for AD are a therapeutic revolution as claimed, and consider that optimism does not excuse a lack of scientific, regulatory, and ethical integrity. We argue for rigorous, properly controlled (e.g. donepezil) anti-amyloid trials demonstrating cognitive and functional benefit before accepting amyloid-lowering drugs as the new standard of care for AD patients.

Key words: ethics, clinical trials, bias, Alzheimer's disease, amyloid hypothesis

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Introduction

After 20 years since the approval of memantine, some novel drugs have been introduced for the treatment of patients with Alzheimer's disease (AD) beginning in late 2021. In clinical trials, these drugs, Aduhelm (aducanumab), Leqembi (lecanemab) and Kisunla (donanemab), all of which are monoclonal antibodies against amyloid-β (Aβ) peptides made of 39–43 amino acids which make up the amyloid in the brain and elsewhere in the body, have been found to reduce Aβ on a positron emission tomography (PET) scan in the brain.[1]

Based on this scientific achievement and a statistical delay of cognitive decline, they have been applauded as wonder drugs amidst a backdrop of rhetoric suggesting that the AD treatment landscape is undergoing substantive transformation.[2] However, their effect on reducing cognitive decline remains beyond clinically-meaningful detection, whereas what are frequently visible, though often treated as a footnote, are their adverse side effects that include brain edema and microhemorrhages, which can, in rare instances, be fatal.[3] We have previously argued that survival time is an important factor in determining the therapeutic value of these and other drugs for long-term use in AD.[4] On the back of recent scandals of scientific image manipulation and controversial decisions made by drugmakers, we continue our critique of over-reliance on amyloid-lowering as a therapeutic strategy in AD.

In this editorial, we examine these issues in detail. In particular, we wish to argue that there is a community-wide bias towards these drugs which facilitates a lack of scientific, ethical and regulatory integrity that does disservice to the growing community affected by AD.

The amyloid hypothesis: an elegant engine to motivate clinical trials

According to the famous amyloid cascade hypothesis (ACH), AD is caused by the sequential deposition of proteins that define the disease, Aβ and tau. Amyloid is thought to act as an upstream "trigger", whereas tau is the "bullet" of AD pathogenesis.[5] We recognize the strength of the evidence in favor of the ACH from genetics and neuropathology of the early contemporary history of AD research.[6] Moreover, the ACH has contributed to significant experimental and conceptual progress in the field by motivating thousands of experiments and dozens of clinical trials testing its central claim, as well as providing a rich conceptual toolkit to protect it from empirical refutation.[7]

Here, our concern is what Nguyen calls "the seductions of clarity".[8] In other words, because the ACH provides an elegant explanation of AD, it must be right. We worry that the ACH's elegance has taken precedence over evidence in favor of the amyloid-lowering therapeutic strategy. Thus, the ACH may be "a conclusion in search of support",[6] instead of the other way round. For instance, if we take the example of the re-definition the disease itself as a biological entity, "AD = A+T+N+"[9] – where A+ stands for biomarkers of amyloid, T for tau, and N for neurodegeneration, this essentially summarizes the hypothetical amyloid cascade (A→T→N), suggestive of the role of this hypothetical explanatory schema in defining the disease itself. In 2024, it is now possible to diagnose AD in A+ people alone,[10] though this idea has provoked much controversy among neurologists.[11]

However, the ACH could be wrong. Prior to 2021, all clinical trials lowering amyloid had failed to improve or even succeeded in worsening AD patients' cognition.[12] All such trials were resting on the assumption that amyloid-β is an underlying cause of AD. This idea has certainly evolved since the early 2000s, but has not undergone anything like a paradigm shift.[7] In 2011, Castellani and Smith[13] noted:

> *With each failure of anti-amyloid-β therapy in clinical trials, new trials are initiated with no hint of slowing down [...]. With dozens of clinical trials targeting amyloid-β either under way or having failed, and with no signs of slowing down, a legitimate concern is that the hypothesis has become 'too big to fail'. With so much time, money and, indeed, faith invested in the construct, is a negative outcome simply intolerable for the scientific community and society who depends on it?*

More recent criticism – including our own – against over-reliance on monoclonal Aβ antibodies as a therapeutic strategy in AD, is thus not novel, but an iteration of earlier attempts to expose what should be regarded as over-reliance on a seductive idea.

Recent hope from amyloid-lowering trials in AD has been provided by results from clinical trials. Patients treated with infusions of lecanemab over 18 months had a worsening of the CDR-SB cognitive scoring system by 1.21 points, while placebo worsened 1.66 points, and the relative difference between these two is 27% (0.45 points), less than half the level of minimal clinical relevancy of at least 1–2.5 points, and similar to other drugs of the same category as lecanemab, which on average produce a 0.18 point difference according to the largest meta-analysis yet of amyloid-lowering clinical trials.[3] Yet as Kurkinen[14] states:

> *1.21 and 1.66 are not measured values of the study population with and without lecanemab but are calculated ... as a weight-adjusted change from the data for men and women. Isn't this like comparing apples and oranges? Clearly, a −0.73 difference for men and a −0.20 for women [...] are too different to originate (statistically) from the same population. Therefore, I suggest that 1.21, 1.66 and −0.45 do not represent*

any population, do not characterize anybody, have no meaning, and are useless value … commentaries and popular media have interpreted the −0.45 difference as a 27% (0.45/1.66) less cognitive decline in the lecanemab group compared to the placebo group. This is a very trivial miscalculation. The correct value is 9.3% (0.45/4.86), which pays attention to the 3.2 baseline.

However, listening to its advocates gives the impression that the ACH has finally been vindicated after a decades-long search that never truly questioned the target, but the trials testing them.

The pathologization of Aβ PET scans in AD

As of 2024, the Alzheimer's Association workgroup considers a positive amyloid PET scan to be sufficient for diagnosis, suggesting the separability of AD and dementia.[10] This rethink of the AD concept has ushered in "a fundamental shift from syndrome-based Alzheimer's dementia care to early, biomarker-guided treatment of Alzheimer's disease".[15] On the front line of this shift, a recent class of "high-clearance anti-Aβ antibodies" has been approved in different health systems, including the USA – aducanumab, lecanemab, and donanemab.[1]

These antibodies provide a set of powerful immunotherapies that significantly reduce Aβ on PET scans, while also modifying the brain's highly sensitive and coordinated immune response, inducing severe neuronal disturbances.[16] The precedent for the approval of these drugs was set on June 7, 2021, when the U.S. Food and Drug Administration (FDA) approved aducanumab (Aduhelm®; Biogen, Cambridge, USA), the first new drug in 18 years for the treatment of patients with AD, citing the "evidence that Aduhelm reduces amyloid beta plaques in the brain and that the reduction in these plaques is reasonably likely to predict important benefits to patients".[17] This drug would then be withdrawn in 2024 amidst a backdrop of rhetoric about its supposed importance to research as a "groundbreaking discovery".[4] Nevertheless, lecanemab and donanemab would fare better in different health systems on the way to almost universal approval.

However, recent literature has brought serious question marks as to whether the PET-signals captured in the clinical trials testing these monoclonal anti-Aβ antibodies are misinterpreted as Aβ clearance, rather than general brain shrinkage and tissue damage. Høilund-Carlsen et al.[18] observe that

…decreased amyloid PET signal in these trials is unlikely to be a one-to-one reflection of amyloid removal, but rather a reflection of increased therapy-related brain damage, as supported by the increased incidence of ARIAs and reported loss of brain volume […]. [The authors therefore] fear that reported decreases in cerebral amyloid deposits more likely reflect decreased uptake of unspecific amyloid PET tracers.

This leads the authors to question the use of amyloid PET as a single primary outcome measure for anti-amyloid treatments and argue that outcome data in these studies should therefore be supplemented with brain magnetic resonance imaging (MRI) scans, to show the effect of the drugs on brain size and atrophy.[19] Given the uncertainties about the meaningfulness of statistical delays in cognitive decline, PET Aβ reduction, as well the possibility of side effects, we argue that language used to describe the therapeutic relevance of reducing PET Aβ with anti-Aβ antibodies in AD should be based on a sober interpretation of clinical trial data.

Indeed, the concept of "ARIA," short for Aβ-related imaging abnormalities, emerged to describe treatment-related brain edema and hemorrhage seen in MRI of AD, particularly following Aβ-lowering. ARIA represents 2 phenomena: edema (ARIA-E) and hemorrhage (ARIA-H). ARIA-E or cerebral edema results from the accumulation of fluid due to the opening of the blood–brain barrier.[20] Symptoms common to ARIA-E and ARIA-H include headache, confusion, dizziness, nausea, tremor and gait disturbances. ARIA-H occurs frequently in the aging population and AD patients, whereas ARIA-E is more specifically related to amyloid-lowering.[21]

The phenomenon of ARIA has variable severity as detected by MRI depending on different background factors. Approximately half of AD patients have what is known as cerebral amyloid angiopathy (CAA), in which Aβ accumulates in the walls of cerebral arteries.[22] When antibodies remove Aβ from the walls of blood vessels, the weakened vessels increase a person's susceptibility to edema, hemorrhage and mortality in more severe cases.[23] Other risk factors include the use of anticoagulant drugs, and also apolipoprotein E (*APOE4*) genotype, a risk factor for dementia.[24]

Moreover, lecanemab did not appear to slow cognitive decline in *APOE4* carriers, and appeared to accelerate decline in participants with 2 copies of the *APOE4* gene.[14] Most people with symptomatic AD carry 1 or 2 copies of the *APOE4* gene, limiting the impact of amyloid PET-lowering drugs outside of clinical trials.[25]

A meta-analysis found that one related effect of anti-amyloid antibodies is accelerated brain atrophy.[26] Belder et al. propose a novel acronym within the emerging AD lexicon: Aβ removal-related pseudoatrophy or "ARPA", a loss of brain volume associated with treatment with Aβ-lowering therapies, which the authors consider not to be harmful.[27]

The acronym "ARIA" was intended to refer to an imaging phenomenon rather than a clinical syndrome.[28] We argue that this is a rhetorical strategy that means that ARIA

cannot be, by definition, a cause of death. Moreover, ARPA differs by 1 letter to ARIA. These are paronyms: words with similar forms, but different meanings. We believe that this rhetorical choice may have been made to make "ARPA" sound more palatable alongside its well-accepted amyloid-lowering neighbor, ARIA. Although acronyms are necessary to standardize language in the scientific literature, they should not trivialize important side-effects.

In summary, the use of anti-amyloid treatments can lead to swelling and bleeding in many cases, sometimes very serious. An important feature of these 2 Aβ-lowering acronyms is how neutral they sound. Yet some cases of ARIA can be very serious and result in death due to related causes, and further data will ultimately determine ARPA's significance. If we return to the contrast between the neutral-sounding lexicon of PET Aβ-lowering (ARIA and ARPA) with the lexicon of PET Aβ increase, the new biological diagnostic criteria of the Alzheimer's Association working group considers a positive Aβ-PET scan to be sufficient for diagnosis of biological AD, a "pathogenic condition".[10] Yet, most asymptomatic Aβ-positive individuals who have "biological AD" will not actually develop dementia in their lifetimes, shedding doubt on the usefulness of a potentially harmful label to patients in the absence of cognitive decline.[29] We consider that this asymmetry that pathologizes PET Aβ accumulation and banalizes side effects of PET Aβ lowering is suggestive of bias in the language used to talk about AD towards the amyloid-lowering strategy.

Doubts about scientific, ethical and regulatory integrity

Going back to our point about seductive clarity and amyloid, we wish to first draw attention to a hot topic in AD and neuroscience research: image manipulation, or the faking of research findings. In AD research, so far these relate to a fake amyloid oligomer Aβ*56[30] and dozens of further manipulated papers supporting the amyloid-lowering strategy.[31] We do not claim that these findings directly refute the ACH. But they do raise concern about the vulnerability of those seduced by the ACH's clarity and how it may have led them to fake images in favor of the ACH, "a conclusion in need of support".[6] Whatever the reasons and pressures that led leading scientists to manipulate their images, it means that the ACH evidence base is now partly lacking in scientific integrity.

However, integrity issues in the field extend beyond preclinical science to the ethics of clinical research. In trials of both lecanemab and donanemab, *APOE4* genetic tests showed that certain patients were predisposed to ARIA if they took the drugs, but these participants were not informed, creating a recent scandal in the lay press in the *New York Times*.[32] We consider this withholding of genetic risk for ARIA to be a violation of Paragraph 26 of the Declaration of Helsinki,[33] which states:

> *In medical research involving human participants capable of giving informed consent, each potential participant must be adequately informed in plain language of the aims, methods, anticipated benefits and* ***potential risks and burdens****.*

We draw on the "social value requirement for clinical research", where social value is understood as "collecting data which might be used to improve health"[34] to ask the question: why did drug developers, who aim to improve health, not share genotype data they knew to have a significant impact on participants' health, i.e., data with high social value to those people who could use them to make informed decision to continue or forego participation?

Beyond this hard violation of informed consent, there are also widespread soft violations of providing inaccurate information about the risk-benefit profile of these antibodies on the part of clinicians and advocates, based on seductive language used to describe the effects of anti-amyloid antibodies as giving people more time with their loved ones, despite the fact that this claim is not backed up by data from clinical trials.[35] For instance, on September 12, 2024, the leading AD scientist Henrik Zetterberg published an article in *Nature*.[36] We consider that this clinician-scientist and industry-backed key opinion leader has overstated clinical facts and made ungrounded claims about the drug. Zetterberg states that the drug can "buy a person invaluable months or years to spend with loved ones before dementia sets in". As another example, in the above *New York Times* piece,[32] a leading Alzheimer's Association spokesperson repeats this "precious time bought" narrative:

> *I think it's transformational. It is not a cure. We understand that. And it has side effects. So it may not be for everyone. But for those that could benefit, it offers more time during the most critical stage where you're still independent, you still have a lot of opportunity to enjoy time with family, baptisms, weddings, graduations.*

As alluded to above, we consider these to be misguided claims. As Professor Robert Howard, an old age psychiatrist specializing in dementia argues[37]:

> *The benefits of lecanemab are so modest as to be undetectable in an individual treated patient. Although 27% slowing of disease course sounds impressive, this is not strictly what the analysis of the trial data showed. It's important the results are discussed honestly, accurately and without spin.*

Without truthful reporting of the risks and benefits of these drugs for individuals, truly informed consent is not possible.[35] But beyond the problem of informed consent, let us turn to the use of placebo, since Paragraph 33

of the World Medical Association (WMA) Declaration of Helsinki[33] explicitly states:

> *The benefits, risks, burdens, and effectiveness of a new intervention must be tested against those of the best proven intervention(s) […]. Extreme care must be taken to avoid abuse of this option.*

Several cholinesterase inhibitors have received full approval for use in early AD, which is the disease stage at which the tests of lecanemab and donanemab were conducted.[38] However, in neither the lecanemab nor the donanemab trial were cholinesterase inhibitors administered systematically, but instead used as part of the randomization criteria. As measured by ADAS-Cog 14 or CDR-SB, the slowing of cognitive decline accomplished by lecanemab at 18 months was only half of that achieved by the vastly cheaper donepezil by only 6 months.[39] If anti-amyloid antibodies are indeed disease modifying, then they should have lasting effects on the disease course regardless of the supposedly symptomatic effects of previously-approved drugs. Finally, the use of inactive placebo as a control may have led to unblinding effects due to ARIA, since on more objective measures of cognition, the effect size of antibody treatment was lower.[40]

Drug sponsors have an ethical duty to inform research participants of genetic profiles, risks and benefits, and also to test these antibodies against the standard of care[4] via "head-to-head" comparisons with available treatments, none of which seem to be a priority for drug developers.[3]

Here, we make a final point about conflicts of interest. A US Congressional report found that the FDA's relationship with sponsor Biogen during approval process of Aduhelm was "atypical and failed to follow the agency's own documentation protocol", and a recent BMJ inquiry found that the FDA committee that approved donanemab contained conflicts of interest.[41] The European Medicines Agency (EMA), who initially rejected lecanemab in July 2024, has a no-tolerance policy on conflicts of interest in their advisory board. However, after re-considering the data with "excluded data from 274 patients who carried 2 copies of the *ApoE4* gene and were therefore at highest risk of ARIA", as well as "submissions from patients, carers, clinicians and professional organizations, who shared their perspectives on the unmet needs of patients with Alzheimer's disease and the data on cognitive decline and risks", the EMA also recommended approval for use in early AD with *ApoE ε4* non-carriers or heterozygotes in November 2024.[42] It is not clear whether any of the groups in the "re-examination procedure" had conflicts of interest. We believe that advocacy from industry-backed leaders like Zetterberg will have certainly played a role in the change of decision. Nevertheless, other researchers have reported difficulties when contacting the EMA for information regarding conflicts of interest.[43]

However, the financial interests of these companies (Biogen, Eisai and Eli Lilly & Company) extend into drug advocacy in patient organizations, such as the Alzheimer's Association, whose 2023 Annual Report states that Eli Lilly and Eisai (the primary sponsors of donanemab and lecanemab, respectively) donated between $500,000 and $999,999, whereas Biogen (the secondary sponsor of lecanemab) donated between $250,000 and $499,999. We are concerned that this industry-backed advocacy is based on a foregone conclusion, inspired by over-reliance on the ACH, that lowering amyloid PET is ultimately the best strategy available for finding a treatment for AD. We consider that amyloid-lowering should not distract us from the need to explore more treatment avenues in the AD pipeline, which is full of potential treatments that have a variety of non-amyloid and tau targets.[44]

Conclusion

The ACH has long been believed to be the code that would crack the enigma of age-related pathological cognitive decline, and the Alzheimer's Association 2024 workgroup's criteria for biological AD[10] essentially write the ' amyloid→tau→neurodegeneration' hypothetical cascade into history. Here, we remind readers that for cognitively-unimpaired older adults, being amyloid-positive on a PET scan means being in a state of risk, such that converting to dementia is the exception rather than the rule.[29]

In an interview,[45] the geriatrician Jason Karlawish discusses an advert by Biogen (sponsor of Aduhelm and Leqembi), "ID AD: Identify Alzheimer's earlier." The ad portrays a middle-aged man, and from above, white paint is being poured over half of his head, and has closed his covered eye. Below him, the ad reads: "Our understanding of Alzheimer's disease is evolving. So should the way we manage it." The paint represents amyloid build-up on the brain, and as Karlawish points out:

> *The ad by Biogen … depicts a person with an amyloid image that looks like the living dead, "The Phantom of the Opera", in which half the person's face looks like a skull and the other half looks alive. That's not the kind of imagery that's going to help us respect the person, recognize the mind of the person living with Alzheimer's disease.*

The "tragedy discourse"[46] of AD can be seen in the aforementioned New York Times piece in a quote from a researcher at the Alzheimer's Drug Discovery Foundation[32]: "People are robbed of everything that makes them human […]. They're like infants in a human body." We worry that the tragedy discourse of AD[46] has contributed to the above non-respect of the rights of people with dementia as research participants with a right to informed consent.

Absent longer, more rigorous tests of amyloid-lowering treatments that emphasize clinical endpoints, respect informed consent and test antibodies against approved drugs for AD, we therefore argue for a scientific and

ethical reassessment of PET amyloid-lowering treatments. We argue for rigorous, properly controlled (e.g., donepezil) anti-amyloid trials demonstrating long-term cognitive and functional benefit before accepting amyloid-lowering drugs as the new standard of care for AD patients. Given the limited resources available for health care and research, the "high-tech" approach to dementia prevention should not distract away from cost-effective "low-tech"[47] action to rethink ambitious public health action against behavioral and social determinants of brain health.[48]

We do not deny the impact of dementia on selfhood, relationships and well-being that urgently requires safe and effective treatments. But we urge researchers, advocates and regulators to put the rights of people living with dementia before the promotion and testing of ideas so as to "promote, protect, and ensure the full enjoyment of human rights by persons with disabilities" as articulated in the UN's Convention on the Rights of Persons with Disabilities,[49] in force in 186 countries. We close with a quote by philosopher Jiddu Krishnamurti,[50] who mentioned a trap humankind can fall into in both daily life and hypothesis-driven science:

> *We sacrifice the present for the future – and it does not matter what means we employ as long as our declared purpose is to produce a result which we say will be beneficial to man. Therefore, the implication is that a wrong means will produce a right end and you justify the wrong means through ideation.*

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