

Alzheimer's trials: A cul-de-sac with no end in sight

Markku Kurkinen^{D,F}

NeuroActiva™, Inc., San Jose, USA

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;

D – writing the article; E – critical revision of the article; F – final approval of the article

Advances in Clinical and Experimental Medicine, ISSN 1899–5276 (print), ISSN 2451–2680 (online)

Adv Clin Exp Med. 2021;30(7):653–654

Address for correspondence

Markku Kurkinen

E-mail: markku@genetics.wayne.edu

Funding sources

None declared

Conflict of interest

None declared

Acknowledgements

I thank Manuel Graeber, Anna Thuring, Jack de la Torre and Lloyd Tran for their interest and comments.

Received on June 21, 2021

Accepted on June 28, 2021

Published online on July 27, 2021

Cite as

Markku Kurkinen. Alzheimer's trials: A cul-de-sac with no end in sight. *Adv Clin Exp Med*. 2021;30(7):653–654. doi:10.17219/acem/139501

DOI

10.17219/acem/139501

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This is an article distributed under the terms of the Creative Commons Attribution 3.0 Unported (CC BY 3.0) (<https://creativecommons.org/licenses/by/3.0/>)**Key words:** Alzheimer's disease, clinical trials, drug discovery, EAAT2

Understanding and treatment of disease go hand in hand. A case in point, the topic of this Editorial, is Alzheimer's disease (AD), a most devastating disorder of the human mind and the major cause of dementia. Despite decades of research efforts in academia and the drug industry, and hundreds of clinical trials, we have no cure, no prevention and no treatment for AD. Why is that? The short answer is that we do not understand AD – its origin and disease mechanisms.

The long answer is as follows. In the early 1900s, when Alois Alzheimer and many others described amyloid plaques and neurofibrillary tangles in the postmortem brains of senile people, they did not propose any cause or effect. Do the plaques and tangles cause dementia, or does dementia cause the plaques and tangles? Indeed, in 1911 Alzheimer wrote: "There is then no tenable reason to consider these cases as caused by a specific disease process."¹ The amyloid hypothesis proposes A β peptide accumulation and amyloid formation in the brain cause AD. The hypothesis has almost singularly guided AD research and clinical trials ever since it was formulated 30 years ago.² Yet, several facts, and experimental studies, are against the hypothesis.^{3–8} All AD trials, hundreds of them over the years, whether with β - or γ -secretase inhibitors to reduce A β peptides production or with anti-A β antibodies to clear amyloid from the brain, have failed to stop or slow cognitive decline or improve daily living of AD patients. Similarly, in preventive trials in cognitively unimpaired people at high risk of developing AD, due to the *APOE4* gene or elevated PET scan-determined brain amyloid, reducing A β peptide production and amyloid did not prevent or slow cognitive decline. The most definitive evidence against the hypothesis, however, comes from the recent preventive trials in cognitively unimpaired people carrying the presenilin *PS1* mutation E280A, which causes AD at age 45. Trials with the anti-A β antibodies solanezumab or ganterumab failed to prevent or slow cognitive decline. Even worse, the preventive trials and treatment methods intended to help often harmed many study participants volunteering for the trials by causing serious health problems, including enhanced cognitive decline.

If these AD trials and failures do not prove the amyloid hypothesis wrong, then what does? And if these trials and errors do not ring the bell and call for a major change in AD research, and question the rationales of AD research policy making, then what does?

It is fair to say the absence of disease-modifying treatments for AD today is due to the amyloid hypothesis, a misguided hypothesis of AD etiology, which

has dominated research, drug development and clinical trials for 30 years. In 2014, when Jack de la Torre was writing in *The New England Journal of Medicine*: “[...] when is a dead hypothesis really dead?”, he was commenting on the failed trials in AD patients with the anti-A β antibodies solanezumab and bapineuzumab.⁹ However, the hypothesis is not dead yet, as exemplified by the recent resurrection of clinical trials with aducanumab.¹⁰ On June 7, 2021, the US Food and Drug Administration (FDA) approved the use of aducanumab (Aduhelm™) to treat AD.¹¹

In 1991, Swash et al. wrote: “Recent advances in Alzheimer's disease imply a need for adequate clinical trials of new treatments which require careful design.”¹² Today, recent advances in AD research have investigated astrocytes, synaptic function and glutamate signaling. In neurotransmission, synaptic glutamate signaling is regulated by the glutamate transporter EAAT2 expressed on astrocytes (which cover the synapses). As soon as glutamate signaling starts, it is stopped within 1 ms by EAAT2, which binds and removes glutamate from the synapses. This prevents excessive glutamate signaling, which can lead to synapse loss and neuron cell death, the early signs of developing AD. In mouse models of AD, increasing EAAT2 expression slows disease progression, whereas decreasing EAAT2 expression enhances disease progression. Human postmortem AD brains have less EAAT2. These observations, and many other studies, indicate EAAT2 as a promising target in drug discovery and clinical development for novel therapies in AD and other neurological and psychiatric diseases.^{13–15}

ORCID iDs

Markku Kurkinen  <https://orcid.org/0000-0002-4483-5101>

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