Lecanemab (Leqembi) is not the right drug for patients with Alzheimer's disease

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Abstract

On July 6, 2023, the U.S. Food and Drug Administration (FDA) approved lecanemab (Leqembi) for the treatment of Alzheimer's dementia (AD) patients. In 2 clinical trials, lecanemab reduced amyloid in the brain and slowed cognitive decline. Here, I review in detail the clinical trial by van Dyck et al. (2023) entitled "Lecanemab in early Alzheimer's disease", published in *The New England Journal of Medicine* on January 5, 2023. In this 18-month trial, lecanemab did not slow cognitive decline in women. This is especially significant because women have a twofold increased risk of AD compared to men, that is, there are 2 times more women than men living with AD. Lecanemab did not slow cognitive decline in *APOE4* carriers; rather, it enhanced the decline in study participants with 2 *APOE4* genes. This is bad news for AD patients, 60–75% of whom carry at least 1 *APOE4* gene. These negative results regarding lecanemab's therapeutic value make me wonder if the approval of lecanemab was the worst decision of the FDA up till now, after the approval of aducanumab on June 7, 2021.

Key words: immunotherapy, clinical trial, Alzheimer, lecanemab, *APOE4*

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Introduction

Lecanemab (branded Leqembi by Eisai and Biogen) is a monoclonal antibody targeting oligomeric Aβ peptides, which prevents amyloid formation.[1] In 2 clinical trials, lecanemab reduced amyloid deposits in the brain and slowed cognitive decline in early Alzheimer's dementia (AD) patients, as reported in 3 papers.[2–4] On July 6, 2023, The U.S. Food and Drug Administration (FDA) approved lecanemab for the treatment of AD patients,[5] following the Advisory Committee's endorsement by a 6-0 vote on June 9, 2023. In this commentary, I review the clinical trial study by van Dyck et al.[4] "Lecanemab in early Alzheimer's disease", published in *The New England Journal of Medicine* on January 5, 2023 (online November 28, 2022), by a way of telling two stories called "Apples and Oranges" and "*APOE4*". Further, I opine on the unusual and less than transparent fashion, to say the least, on how the results were disclosed, presented, interpreted, and discussed in van Dyck et al.'s paper.

Objectives

The purpose of the study was to review, re-analyze and re-interpret the clinical trial results of lecanemab that can be found in the paper and supplementary appendixes published by van Dyck et al.[4] Additionally, I aim to question the lecanemab's estimated 27% clinical benefit in slowing AD progression, when a better estimate is 9.3%, and to question the treatment of men and women as one 'statistical' population, when their responses to lecanemab were too different to happen by chance.

Apples and oranges

Table 1, which is adapted from Figure S1B (van Dyck et al., Supplementary Appendix),[4] shows mean changes of CDR-SB (Clinical Dementia Rating–Sum of Boxes) scores from baseline to 18 months and percent slowing of cognitive decline for men and women with and without lecanemab. Now, let us define (Equation 1):

$$x - y = z \quad (1)$$

Table 1. CDR-SB score change with and without lecanemab

APOE4	Number of participants (placebo, lecanemab)	Adjusted mean change	Percent slowing of decline
–/–	275, 267	–0.75	41
–/+	468, 456	–0.50	30
+/+	132, 136	0.28	–22
Female	446, 441	–0.20	12
Male	411, 416	–0.73	43

The content of the table is adapted from van Dyck et al. (Figure S1B, Supplementary Appendix).[4] Adjusted mean change (from baseline to 18 month) is the Clinical Dementia Rating–Sum of Boxes (CDR-SB) score difference of the lecanemab minus the placebo-treated group, negative difference indicating benefit of lecanemab treatment. The CDR-SB measures cognition and function on an 18-point scale, higher scores indicating worse performance.[6] Percent slowing of decline (of cognition and function) is calculated as score difference divided by placebo score.

where x indicates the lecanemab score, y stands for the placebo score and z represents the difference.

Let us define (Equation 2)

$$z/y = \% \text{ slowing} \quad (2)$$

where score difference divided by placebo score (multiplied by 100) gives percent slowing of cognitive decline with lecanemab compared to placebo.

From the data in Table 1, we can now calculate (*calculemus*, as Leibniz would say) x- and y-scores for men and women, as shown below

MEN 47.7%	**WOMEN** 52.3%
x – y = –0.73	x – y = –0.20
0.73/y = 0.43	0.20/y = 0.12
x = 0.97	x = 1.47
y = 1.70	y = 1.67

And from these values, we can calculate men (47.7%) plus women (52.3%) combined weight adjusted x- and y, as follows

MEN+WOMEN

x = 0.477 × 0.97 + 0.523 × 1.47 = 1.23

y = 0.477 × 1.70 + 0.523 × 1.67 = 1.68

The combined score difference 1.23 – 1.68 = –0.45 is the difference between the lecanemab and placebo groups reported by van Dyck et al.[4] It can also be derived from weigh adjusted score differences:

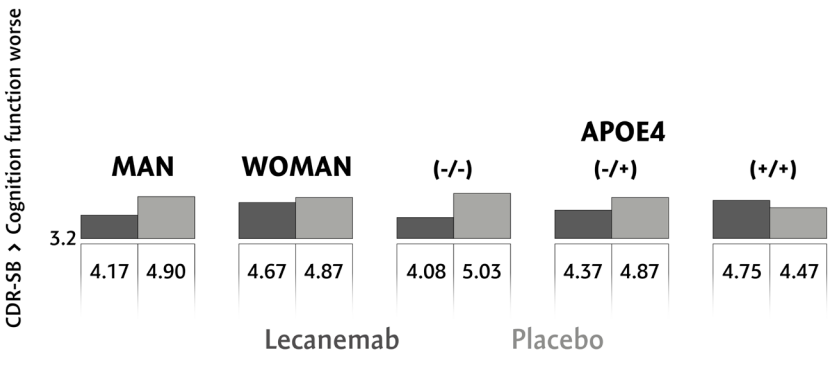

Fig. 1. Lecanemab does not work for women and enhances cognitive decline of *APOE4* (+/+) carriers.

Numbers show CDR-SB score at the end of 18-month trial. Dark grey (lecanemab) and light gray (placebo) bars show score increase from baseline (3.2). The –0.73 difference for men indicates 14.9% (0.73/4.90) less disease progression and cognitive decline with lecanemab compared to placebo, and the –0.20 difference for women indicates 4.1% (0.20/4.87) less decline. Score differences for the *APOE4* carriers indicate 18.9% (–/–), 10.3% (–/+) and –6.3% (+/+) less cognitive decline

0.477 × (–0.73) + 0.523 × (–0.20) = –0.455.

And finally, z/y = 0.45/1.68 = 26.8% slowing.

Accordingly, for men plus women, the score change was 1.23 with lecanemab and 1.68 without lecanemab, with a difference of –0.45. Note how these values are described in the paper: "The adjusted least-squares mean change from baseline at 18 months was 1.21 with lecanemab and 1.66 with placebo (difference, –0.45; 95% confidence interval [CI], –0.67 to –0.23; p < 0.001)."[4]

Importantly, although not explicitly stated, 1.21 and 1.66 are not measured values of the study population with and without lecanemab but are calculated (the way I did above) 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 (Table 1) 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 values.

Now, let's look at Fig. 2 in the van Dyck et al.'s paper,[4] which shows data on the aggregate of brain amyloid positron emission tomography (PET) and several other cognitive measures as an adjusted mean change from baseline in the study populations with and without lecanemab. Similar to the CDR-SB score changes discussed above, those cognitive measures apply to nobody or no group in particular, and therefore are useless and irrelevant in the real world.

Further, although not stated in the paper, 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, as observed in Kurkinen et al.[7] The 9.3% less cognitive decline is unlikely to make any difference for people living with early AD.[8]

APOE4

The *APOE4* is the strongest and most common inherited genetic risk factor for AD. Since 1993, it has been known that *APOE4* enhances the development and progression of AD. This conclusion can be deduced from the observation that *APOE4* lowers the age of onset and increases the risk of AD.[9–11] One *APOE4* gene (12% of the population) increases the AD risk by twofold and 2 genes (2%) increase the AD risk by 12-fold compared to *APOE3* carriers (68%).

From the data in Table 1, we can calculate x and y values for the *APOE4* carriers (not shown), and then on top of baseline (3.2), the scores at the trial end (the scores actually measured), as shown in Fig. 1. Note that lecanemab increases CDR-SB scores (making cognition and function worse) in the (–/+) and (+/+) carriers compared to (–/–) carriers, and even enhances cognitive decline of the (+/+) carriers compared to placebo. This has implications for the treatment of AD patients, 60–75% of whom carry at least one *APOE4* gene.[10] This is also bad news for the prevention therapy of individuals at high risk of developing AD associated with 1 (12% of the population) or 2 copies of the *APOE4* gene (2%).

Strangely enough, the *APOE4* gene appears to decrease CDR-SB scores (slowing cognitive decline) in a dose-dependent fashion in the order of (+/+) > (–/+) > (–/–). It has not escaped my attention that between the (+/+) and (–/–) carriers, the score difference is 4.47 – 5.03 (1.27 – 1.83 as increase from baseline) = –0.56, or 11% (0.56/5.03) or 31% (0.56/1.83) slowing of cognitive decline. The difference –0.56 and 31% are better than –0.45 and 27%, the most frequently mentioned clinically meaningful benefit of lecanemab in the treatment of patients with AD.

Wovon man nicht sprechen kann...

The van Dyck et al.'s paper[4] has major problems in how the results are presented, interpreted and discussed. The most conspicuous feature is the lack of reporting the negative results in women and *APOE4* carriers, the majority of the study participants (Fig. 1).

Lecanemab did not work for women (52.3% of the study population), and the CDR-SB score difference between the lecanemab and placebo groups was –0.20 (compared to –0.73 for men). This is especially significant, because women have a 2 times higher AD risk, that is, there are 2 times more women than men living with AD. These data can be found only in Figure S1B in the Supplementary Appendix.[4] Why were these data not disclosed, not even discussed, in the paper? Indeed, the words "man" and "woman" or "male" and "female" were not used, not even once, in the paper.

Lecanemab enhanced cognitive decline in study participants (15.5%) carrying 2 *APOE4* genes, and the CDR-SB score difference between the lecanemab and placebo groups was 0.28. Remarkably, *APOE4* was found to slow cognitive decline in a dose-dependent fashion, in the order of (+/+) > (–/+) > (–/–), so much that the score difference between the (+/+) and (–/–) carriers was –0.56 or a 31% less decline. These values report better outcomes than –0.45 or 27%, the most frequently mentioned clinically meaningful benefit for AD patients.

Why these results were not disclosed in the abstract, results or discussion of the paper, but were hidden in Figure S1B and passed over in silence? Is it because the data would not stand the light of day? Why these data were not brought up and discussed in public, rather than discussed among "insiders" at Clinical Trials on Alzheimer's Disease (CTAD) conference (San Francisco and online, November 29–December 2, 2022)?[12] It seems ironic that nobody was willing to look at the data in Figure S1B and see the forest for the trees, especially since Fig. S1B also displays data in graphs called, of all things, forest plots.

This strange practice of select reporting of the data and bordering on obstruction of science has resulted in news and commentaries that have only misinformed the public about the lecanemab study and lecanemab's clinical benefit, without any hint of the lack of benefit. Only recently, these and other issues noticed in the van Dyck et al.'s paper[4] were raised in the 4 "Letter to Editor" letters published in *The New England Journal of Medicine* on April 27, 2023.[13] One of the letters was from Valenzuela and Pascual-Leone, who write: "We are concerned about the possible lack of therapeutic efficacy among women in the trial by van Dyck and colleagues."

Discussion

Aducanumab is a monoclonal antibody against a conformational epitope found on Aβ peptides.[14] On June 7, 2021, the FDA approved aducanumab (branded Aduhelm by Biogen) for the treatment of AD. This controversial decision, which was against the FDA's Advisory Committee's 10-0 vote not to approve aducanumab, resulted in a congressional investigation concerning inappropriate contact between the FDA and Biogen during the approval process.[15,16] As of today, Aduhelm has not been approved anywhere else in the world, except the UAE.

In AD trials, several monoclonal antibodies against Aβ peptides, oligomers, fibrils, and amyloids have reduced brain amyloid deposits as detected using PET imaging, but they have not slowed cognitive decline. On the contrary, their use has consistently resulted in significant health problems caused by adverse events due to amyloid-related imaging abnormalities (ARIA), as seen on magnetic resonance imaging (MRI) pictures. They have been associated with brain edema and brain hemorrhages that can be fatal.[17–23] For example, in the lecanemab trial,[4] the most common adverse events were infusion-related reactions (26.4% with lecanemab and 7.4% with placebo), ARIA-H with microhemorrhages, macrohemorrhages, or superficial siderosis (17.3% with lecanemab and 9.0% with placebo), and ARIA-E with brain edema (12.6% with lecanemab and 1.7% with placebo).

Brain amyloid removal using monoclonal antibodies that bind to soluble oligomeric forms of Aβ peptide, but not to deposited β-sheet fibrillar forms of Aβ amyloid plaques, immediately raises 2 questions. How does the amyloid get removed from the brain as measured with amyloid PET imaging and what does the amyloid PET measure? The Aβ amyloid is found in the cortex (a 1.55–3-mm thick tissue made of neuron cell bodies) and around microvasculature associated with cerebral amyloid angiopathy (CAA), which is present in 90% of AD patients.[24] These areas of amyloid deposition are very different than what can be observed with PET imaging. Indeed, as argued by Høilund-Carlsen et al., the specificity and sensitivity of PET in measuring Aβ amyloid in the brain have not been proven.[25]

The idea to use anti-Aβ antibodies in AD immunotherapy is based on the amyloid hypothesis,[26,27] which proposes that Aβ peptide amyloid formations in the brain cause AD. Thus, the hypothesis predicts that the removal of brain amyloid provides a treatment for AD patients, and preventing brain amyloid formation inhibits the development of AD.[28] Ever since its formulation in 1991–1992, the amyloid hypothesis has almost singularly misguided AD research, drug development and clinical trials. The amyloid hypothesis has been tested in hundreds of clinical trials and shown to be wrong. While a hypothesis can never be proven right, it can be proven wrong, in theory or by experiment.[29]

Limitations

This study is a review and analysis of the clinical trial results published by van Dyck et al.[4] and has the same limitation as the original study. That is, the 1734 study participants (47.7% men, 52.3% women) were treated as one statistical population, which turned out not to be true. For example, the CDR-SB score change in men was 0.97 with lecanemab and 1.70 without, a difference of −0.73, and for women, it was 1.47 with lecanemab and 1.67 without, a difference of −0.20. The −0.50 difference between men and women in the lecanemab group is more than the −0.45 weight-adjusted mean difference of the men+women population with and without lecanemab. As I have suggested in this study, −0.45 does not characterize anybody, because men with a −0.73 difference and women with a −0.20 difference are too different.

Conclusions

In the USA, 6.7 million people are living with AD, and there are 50 million AD patients worldwide.[30] For the treatment of AD, the FDA has approved aducanumab and lecanemab, 2 anti-Aβ antibodies, and I guess, next year comes donanemab, an antibody against the pyroglutamate form of Aβ found only in amyloid plaques.[31,32] These very controversial decisions by the FDA have not been supported by evidence-based science, and clearly do not "promote, protect, and ensure the full enjoyment of human rights by persons with disabilities", as articulated in the United Nations Convention on the Rights of Persons with Disabilities (CRPD), May 3, 2008, that is in force in 186 nations.

Understanding and the treatment of disease go hand in hand. Despite decades of research efforts in academia and the drug industry and hundreds of clinical trials, we have no treatment or prevention for AD. Why is that? The short answer is that we do not understand AD, its origin and disease mechanisms.[33,34]

It is fair to say the amyloid hypothesis is the reason we have no disease-modifying treatment for AD.[35] Therefore, in the spirit of "prevention is the only cure", we need

to invest more into the research on preventive therapies as well as increase public awareness of the role healthy lifestyles can play in delaying the onset of AD.[36–38]

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References

1. Leqembi. Alzforum: Networking for a Cure; 2023. http://www.alzforum.org/therapeutics/leqembi. Accessed July 20, 2023.
2. Swanson CJ, Zhang Y, Dhadda S, et al. A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aβ protofibril antibody. *Alzheimers Res Ther*. 2021;13(1):80. doi:10.1186/s13195-021-00813-8
3. McDade E, Cummings JL, Dhadda S, et al. Lecanemab in patients with early Alzheimer's disease: Detailed results on biomarker, cognitive, and clinical effects from the randomized and open-label extension of the phase 2 proof-of-concept study. *Alzheimers Res Ther*. 2022;14(1):191. doi:10.1186/s13195-022-01124-2
4. Van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. *N Engl J Med*. 2023;388(1):9–21. doi:10.1056/NEJMoa2212948
5. U.S. Food and Drug Administration (FDA). FDA Converts Novel Alzheimer's Disease Treatment to Traditional App. Silver Spring, USA: U.S. Food and Drug Administration (FDA);2023. http://www.fda.gov/news-events/press-announcements/fda-converts-novel-alzheimers-disease-treatment-traditional-approval. Accessed July 20, 2023.
6. McDougall F, Edgar C, Mertes M, et al. Psychometric properties of the clinical dementia rating: Sum of boxes and other cognitive and functional outcomes in a prodromal Alzheimer's disease population. *J Prev Alzheimers Dis*. 2020;8(2):151–160. doi:10.14283/jpad.2020.73
7. Kurkinen M, Fułek M, Fułek K, Beszłej JA, Kurpas D, Leszek J. The amyloid cascade hypothesis in Alzheimer's disease: Should we change our thinking? *Biomolecules*. 2023;13(3):453. doi:10.3390/biom13030453
8. Lansdall CJ, McDougall F, Butler LM, et al. Establishing clinically meaningful change on outcome assessments frequently used in trials of mild cognitive impairment due to Alzheimer's disease. *J Prev Alzheimers Dis*. 2022;10(1):9–18. doi:10.14283/jpad.2022.102
9. Mahley RW, Weisgraber KH, Huang Y. Apolipoprotein E4: A causative factor and therapeutic target in neuropathology, including Alzheimer's disease. *Proc Natl Acad Sci U S A*. 2006;103(15):5644–5651. doi:10.1073/pnas.0600549103
10. Raulin AC, Doss SV, Trottier ZA, Ikezu TC, Bu G, Liu CC. ApoE in Alzheimer's disease: Pathophysiology and therapeutic strategies. *Mol Neurodegener*. 2022;17(1):72. doi:10.1186/s13024-022-00574-4
11. Mahley RW. Apolipoprotein E4 targets mitochondria and the mitochondria-associated membrane complex in neuropathology, including Alzheimer's disease. *Curr Opin Neurobiol*. 2023;79:102684. doi:10.1016/j.conb.2023.102684
12. Dare we say consensus achieved: Lecanemab slows the disease. Alzforum: Networking for a Cure; 2022. https://www.alzforum.org/news/conference-coverage/dare-we-say-consensus-achieved-lecanemab-slows-disease. Accessed July 20, 2023.
13. Letter to Editor: Lecanemab in early Alzheimer's disease. *N Engl J Med*. 2023;388(17):1630–1632. doi:10.1056/NEJMc2301380
14. Aduhelm. Alzforum: Networking for a Cure; 2023. http://www.alzforum.org/therapeutics/aduhelm. Accessed July 20, 2023.
15. Kurkinen M, Tran L. Aduhelm: The best gope for Alzheimer's disease patients or the worst decision the FDA has ever made? *J Alzheimers Dis*. 2021;84(3):969–971. doi:10.3233/JAD-215105
16. The Committee on Oversight and Accountability (Democrats). Maloney and Pallone Release Staff Report on Review, Approval, and Pricing of Biogen's Alzheimer's Drug Aduhelm. Washington, D.C., USA: The Committee on Oversight and Accountability (Democrats); 2022. https://oversightdemocrats.house.gov/news/press-releases/maloney-and-pallone-release-staff-report-on-review-approval-and-pricing-of. Accessed July 20, 2023.
17. Valiukas Z, Ephraim R, Tangalakis K, Davidson M, Apostolopoulos V, Feehan J. Immunotherapies for Alzheimer's disease: A review. *Vaccines*. 2022;10(9):1527. doi:10.3390/vaccines10091527
18. Perneczky R, Jessen F, Grimmer T, et al. Anti-amyloid antibody therapies in Alzheimer's disease. *Brain*. 2023;146(3):842–849. doi:10.1093/brain/awad005
19. Espay AJ, Herrup K, Daly T. Finding the falsification threshold of the toxic proteinopathy hypothesis in neurodegeneration. *Handb Clin Neurol*. 2023;192:143–154. doi:10.1016/B978-0-323-85538-9.00008-0
20. Castellani RJ, Shanes ED, McCord M, et al. Neuropathology of anti-amyloid-β immunotherapy: A case report. *J Alzheimers Dis*. 2023;93(2):803–813. doi:10.3233/JAD-221305
21. Hampel H, Elhage A, Cho M, Apostolova LG, Nicoll JAR, Atri A. Amyloid-related imaging abnormalities (ARIA): Radiological, biological and clinical characteristics [published online as ahead of print on June 6, 2023]. *Brain*. 2023:awad188. doi:10.1093/brain/awad188
22. Kepp KP, Sensi SL, Johnsen KB, et al. The anti-amyloid monoclonal antibody lecanemab: 16 cautionary notes. *J Alzheimers Dis*. 2023;94(2):497–507. doi:10.3233/JAD-230099
23. Villain N, Planche V, Levy R. High-clearance anti-amyloid immunotherapies in Alzheimer's disease. Part 2: Putative scenarios and timeline in case of approval, recommendations for use, implementation, and ethical considerations in France. *Rev Neurol (Paris)*. 2022;178(10):999–1010. doi:10.1016/j.neurol.2022.08.002
24. Greenberg SM, Bacskai BJ, Hernandez-Guillamon M, Pruzin J, Sperling R, Van Veluw SJ. Cerebral amyloid angiopathy and Alzheimer disease: One peptide, two pathways. *Nat Rev Neurol*. 2020;16(1):30–42. doi:10.1038/s41582-019-0281-2
25. Høilund-Carlsen PF, Revheim ME, Alavi A, Barrio JR. FDG PET (and MRI) for monitoring immunotherapy in Alzheimer disease. *Clin Nucl Med*. 2023;48(8):689–691. doi:10.1097/RLU.0000000000004710
26. Hardy J, Allsop D. Amyloid deposition as the central event in the aetiology of Alzheimer's disease. *Trends Pharmacol Sci*. 1991;12:383–388. doi:10.1016/0165-6147(91)90609-V
27. Hardy JA, Higgins GA. Alzheimer's disease: The amyloid cascade hypothesis. *Science*. 1992;256(5054):184–185. doi:10.1126/science.1566067
28. Haass C, Selkoe D. If amyloid drives Alzheimer disease, why have anti-amyloid therapies not yet slowed cognitive decline? *PLoS Biol*. 2022;20(7):e3001694. doi:10.1371/journal.pbio.3001694
29. Popper K. *The Logic of Scientific Discovery*. London, UK: Routledge; 2010. ISBN:978-0-415-27844-7.
30. 2023 Alzheimer's disease facts and figures. *Alzheimer's & Dementia*. 2023;19(4):1598–1695. doi:10.1002/alz.13016
31. Donanemab. Alzforum: Networking for a Cure; 2023. http://www.alzforum.org/therapeutics/donanemab. Accessed July 20, 2023.
32. Rashad A, Rasool A, Shaheryar M, et al. Donanemab for Alzheimer's disease: A systematic review of clinical trials. *Healthcare*. 2022;11(1):32. doi:10.3390/healthcare11010032
33. Huang Y, Mucke L. Alzheimer mechanisms and therapeutic strategies. *Cell*. 2012;148(6):1204–1222. doi:10.1016/j.cell.2012.02.040
34. Kurkinen M. 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
35. Kurkinen M. Astrocyte glutamate transporter EAAT2 in Alzheimer dementia. In: Pavlovic ZM, ed. *Glutamate and Neuropsychiatric Disorders: Current and Emerging Treatments*. Cham, Switzerland: Springer International Publishing; 2022:229–259. doi:10.1007/978-3-030-87480-3
36. Kurkinen M. The amyloid hypothesis is too good to be true. *Alzheimers Dement Cogn Neurol*. 2017;1(1):1–9. doi:10.15761/ADCN.1000106
37. Yu JT, Xu W, Tan CC, et al. Evidence-based prevention of Alzheimer's disease: Systematic review and meta-analysis of 243 observational prospective studies and 153 randomised controlled trials. *J Neurol Neurosurg Psychiatry*. 2020;91(11):1201–1209. doi:10.1136/jnnp-2019-321913
38. Frisoni GB, Altomare D, Ribaldi F, et al. Dementia prevention in memory clinics: Recommendations from the European task force for brain health services. *Lancet Reg Health Eur*. 2023;26:100576. doi:10.1016/j.lanepe.2022.100576