The Journal of Prevention of Alzheimer's Disease 13 (2026) 100696

Contents lists available at ScienceDirect

The Journal of Prevention of Alzheimer's Disease

journal homepage: www.elsevier.com/locate/tjpad

Considering evoke and evoke+ outcomes for future Alzheimer's disease drug development

In the current issue of the *Journal of Prevention of Alzheimer's Disease*, Drs. Jeffrey Cummings and Philip Scheltens provide a timely and critical review[1] of the recently reported evoke and evoke+ trials [evoke(+)] [2] These two large-scale, randomized controlled Phase 3 studies evaluated the efficacy, safety, and tolerability of daily oral semaglutide for the treatment of biomarker-confirmed early symptomatic Alzheimer's disease (AD). The authors discuss the discrepant signals between promising real-world observational and preclinical data, and the definitive negative results of these clinical trials to address the question: Why did oral semaglutide fail to slow clinical progression despite promising real-world data informing the trial design and secondary trial outcomes suggesting peripheral anti-inflammatory effects. These insights are important not only for the future of glucagon-like peptide-1 receptor agonists (GLP-1RA) like semaglutide, but also for the broader landscape of AD therapeutics targeting neuroinflammation.

The evoke(+) program was supported by real-world data, particularly clinical study observations showing a decreased incidence of dementia among patients with type 2 diabetes (T2D) treated with GLP-1RA [3–9]. A core mechanism of interest for semaglutide is its ability to decrease peripheral inflammation, a feature well-documented in patients with T2D and obesity [10]. The review successfully captures the nuances of this target engagement in evoke(+) by evaluating trial biomarker results, such as high-sensitivity C-reactive protein (hsCRP). While the treatment successfully lowered hsCRP levels, the authors draw attention to a critical disconnect where the participant sample did not demonstrate elevated baseline systemic inflammation. This observation highlights the consideration that modulating an inflammatory pathway that is not pathologically elevated is likely different from treating an active, elevated inflammatory state. Furthermore, the review emphasizes that the relatively low prevalence of cerebrovascular disease and T2D-associated peripheral inflammation at baseline may explain why peripheral suppression of inflammatory markers alone was insufficient to modify the AD trajectory. Thus, the lack of cardiometabolic risk in the participant sample may explain the discrepancy in preceding real-world observations and the evoke(+) studies.

The review also highlights how the clinical design of the evoke(+) studies adapted to the real-world landscape by enrolling large, diverse, and representative samples, utilizing participant and care partner input, and allowing participants to enroll or remain in the study if they started recently FDA approved anti-amyloid monoclonal antibody (MAB) therapies [11,12] These innovations were thought to improve recruitment, participant satisfaction, completion rates, and also to allow for the investigation of the effects of anti-amyloid MAB use. However, the relatively small number of participants initiating anti-amyloid MABs limits the power to examen the effect of this intercurrent event and the effect of combined treatment with GLP-1RA and anti-amyloid MABs remains untested.

Finally, the authors discuss the implications of blood-brain barrier (BBB) penetration for disease-modifying AD therapeutics. Because oral semaglutide has limited central nervous system (CNS) penetrance, cognitive benefits in diabetic populations are likely mediated by treating systemic vascular and metabolic dysfunction and the brain parenchymal concentrations achieved are unlikely to directly modulate neuroinflammatory processes. Accordingly, anti-inflammatory drugs targeting parenchymal neuroinflammatory mechanisms should prioritize agents with significant CNS target engagement.

This review provides critical context for the evoke(+) results that will help the AD research community consider the appropriateness of pursuing further studies to test the effectiveness of GLP-1RA and related drugs for effectiveness in AD and related disorders. Considerations for future studies should include the potential need to enrich for elevated cardiometabolic risk or overt vascular cognitive impairment, the possibility that there may be a synergistic effect of co-treatment with anti-amyloid MABs, and the importance of BBB penetrance profile for central versus peripheral target engagement.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

There was no use of generative AI or AI-assisted technologies in scientific writing or in figures, images and artwork.

Declaration of competing interest

The author declares the following financial interests/personal relationships which may be considered as potential competing interests: APM is a consultant for Johnson & Johnson, and receives research support from grants/contracts with Yale University from NIH, Eli Lilly and Co., Janssen Pharmaceuticals Inc., and Genentech Inc. He is a member of the JPAD editorial board and was not involved in the peer review of this article.

References

[1] Cummings JL, Scheltens P. Evoke (+) trials of semaglutide for early alzheimer's disease: innovations, lessons, and implications. J Prev Alzheimers Dis 2026;13(10): 100677. https://doi.org/10.1016/j.tjpad.2026.100677.

[2] Cummings JL, Atri A, Sano M, et al. Efficacy and safety of oral semaglutide 14 mg (flexible dose) in early-stage symptomatic Alzheimer's disease (evoke and evoke+): two phase 3, randomised, placebo-controlled trials. Lancet 2026;407(10544): 2167–79. https://doi.org/10.1016/S0140-6736(26)00459-9.

https://doi.org/10.1016/j.tjpad.2026.100696
Received 28 October 2026; Accepted 1 November 2026
Available online 15 November 2026
2274-5807/© 2026 The Author. Published by Elsevier Masson SAS on behalf of SERDI Publisher. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

[3] Wium-Andersen IK, Osler M, Jorgensen MB, Rungby J, Wium-Andersen MK. Antidiabetic medication and risk of dementia in patients with type 2 diabetes: a nested case-control study. Eur J Endocrinol Nov 2019;181(5):499–507. https://doi.org/10.1530/EJE-19-0259.
[4] De Giorgi R, Koychev I, Adler AI, et al. 12-month neurological and psychiatric outcomes of semaglutide use for type 2 diabetes: a propensity-score matched cohort study. EClinicalMedicine 2024;74:102726. https://doi.org/10.1016/j.eclinm.2024.102726.
[5] Tang B, Sjolander A, Wastesson JW, et al. Comparative effectiveness of glucagon-like peptide-1 agonists, dipeptidyl peptidase-4 inhibitors, and sulfonylureas on the risk of dementia in older individuals with type 2 diabetes in Sweden: an emulated trial study. EClinicalMedicine 2024;73:102689. https://doi.org/10.1016/j.eclinm.2024.102689.
[6] Siddeeque N, Hussein MH, Abdelmaksoud A, et al. Neuroprotective effects of GLP-1 receptor agonists in neurodegenerative disorders: a large-scale propensity-matched cohort study. Int Immunopharmacol 2024;143(Pt 3):113537. https://doi.org/10.1016/j.intimp.2024.113537.
[7] Norgaard CH, Friedrich S, Hansen CT, et al. Treatment with glucagon-like peptide-1 receptor agonists and incidence of dementia: data from pooled double-blind randomized controlled trials and nationwide disease and prescription registers. Alzheimers Dement (N Y) 2022;8(1):e12268. https://doi.org/10.1002/trc2.12268.
[8] Wang W, Davis PB, Qi X, et al. Associations of semaglutide with Alzheimer's disease-related dementias in patients with type 2 diabetes: a real-world target trial emulation study. J Alzheimers Dis 2025;106(4):1509–22. https://doi.org/10.1177/13872877251351329.
[9] Tang H, Shao H, Shaaban CE, et al. Newer glucose-lowering drugs and risk of dementia: a systematic review and meta-analysis of observational studies. J Am Geriatr Soc 2023;71(7):2096–106. https://doi.org/10.1111/jgs.18306.
[10] Verma S, Bhatta M, Davies M, et al. Effects of once-weekly semaglutide 2.4 mg on C-reactive protein in adults with overweight or obesity (STEP 1, 2, and 3): exploratory analyses of three randomised, double-blind, placebo-controlled, phase 3 trials. EClinicalMedicine 2023;55:101737. https://doi.org/10.1016/j.eclinm.2022.101737.
[11] Sims JR, Zimmer JA, Evans CD, et al. Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. JAMA 2023;330(6):512. https://doi.org/10.1001/jama.2023.13239.
[12] van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. N Engl J Med 2023;388(1):9–21. https://doi.org/10.1056/NEJMoa2212948.

Adam P. Mecca
Department of Psychiatry and Alzheimer's Disease Research Unit, Yale School of Medicine, New Haven, CT, USA
E-mail address: adam.mecca@yale.edu.