The Journal of Prevention of Alzheimer's Disease 13 (2026) 100671

Contents lists available at ScienceDirect

The Journal of Prevention of Alzheimer's Disease

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

Editorial

Opportunities to treat specific populations with repurposed drugs

The publication by Lin et al. [1] demonstrating a reduced risk of overall dementia and unspecified dementia in GLP-1 receptor agonists (GLP-1 RA) users relative to long-acting insulin users in type 2 diabetes (T2D) offers an opportunity to reflect on the repurposing of medications approved for indications other than dementia, and about the populations on which to test prospectively such drugs.

Epidemiology has been used to suggest new therapeutic targets in the field of dementia. For instance, the reduced risk of dementia in persons with arthritis documented by McGeer et al. [2] has led to a number of randomized clinical trials (RCT) with various types of anti-inflammatory drugs, so far without success. Ternhamar et al. [3] demonstrated that early use of statins in persons with T2D is associated with lower risk of all-cause dementia after 10 years. Tang et al. [4] have summarized conclusions from observational studies and found that newer glucose lowering drugs were associated with a decreased risk of all-cause dementia in people with T2D. It was thus logical to try semaglutide in two randomized, placebo-controlled trials in early Alzheimer's disease (AD), one of the two trials enriched with persons carrying a higher vascular burden [5]. Unfortunately results were negative towards the slowing of clinical progression using CDR-SB.

Can we improve translation from clinical epidemiology to clinical trials and practice? One approach is to broaden the periodic review of candidate drugs such as that published by Corbett et al. [6]. Another approach to which CTAD and partner organizations can contribute is a discussion about trial designs and outcomes for the populations most likely to benefit from a specific drug class (such as persons with T2D when testing a GLP-1 RA). New evidence from an observational study in T2D cognitively unimpaired populations reveals a pattern of cortical atrophy different from AD [7], possibly leading to different strategy about measuring rate of neurodegeneration on treatment (such as whole brain rather than temporal regions). The primary outcome could be time to dementia defined clinically, rather that the CDR, in a survival design over a minimum of three years for persons randomized at the MCI stage, with stratification using plasma pTau217 levels. Such an approach may bring us closer to treating all-cause dementia.

CRediT authorship contribution statement

Serge Gauthier: Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: SG is a member of SAB with AbbVie, Alzheon, AmyriAD, CaspAid, Eisai Canada, ENIGMA USA, Lilly Canada, TauRx.

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https://doi.org/10.1016/j.tjpad.2026.100671
Received 31 August 2026; Accepted 2 September 2026
Available online 12 September 2026