Semaglutide Potential in Mitigating Alzheimer's Disease Pathology

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Introduction

•**Alzheimer's Disease:** A major neurodegenerative disease affecting 11.5 million Americans. Alzheimer's is the most common cause of dementia. It's characterized by progressive cognitive decline, abnormal protein clumping (amyloid-beta and tau, and chronic inflammation in the brain.

•**Current Treatments:** Existing therapies provide only modest symptom relief and have not consistently demonstrated an ability to slow disease progression. This is because Alzheimer's is a complex disease driven by multiple interacting pathological processes.

•**The Diabetes Connection:** Epidemiological studies show that type 2 diabetes increases the risk of Alzheimer's. It's believed that insulin resistance and poor blood sugar control lead to chronic inflammation in the body, which then triggers and worsens inflammation in the brain.

•**The Role of GLP-1 Agonists:** Glucagon-like peptide-1 (GLP-1) receptor agonists have been investigated as potential therapeutic agents. Preclinical studies suggest they can reduce brain inflammation and support neuronal survival.

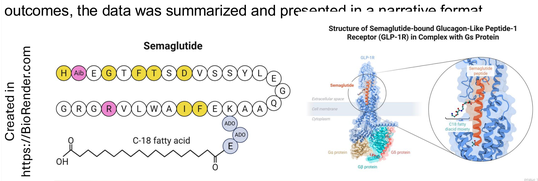
•**Semaglutide's Promise:** These findings have led to interest in repurposing semaglutide for Alzheimer's. By targeting pathways involved in both metabolic dysfunction and neuroinflammation, semaglutide may offer a way to modify the disease's progression, not just its symptoms.

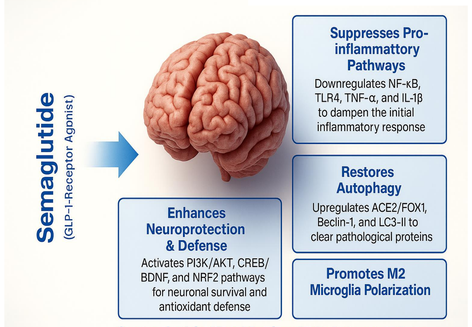
Methodology

•**Search Strategy:** We conducted a systematic search across three major databases: Web of Science, Embase, and Ovid MEDLINE. The search used keywords like "semaglutide" combined with terms related to Alzheimer's disease, such as "dementia" and "cognitive impairment." We used both free-text terms and controlled vocabulary (MeSH and Emtree) to ensure a thorough search.

•**Inclusion Criteria:** The search was limited to English-language publications but included all study types to capture all relevant preclinical and clinical data. Studies were selected if they looked at semaglutide's effects on Alzheimer's pathology, cognition, or neuroinflammation.

•**Data Analysis:** We screened all titles and abstracts to identify potentially relevant studies, then reviewed the full texts. Because the studies had different designs and outcomes, the data was summarized and presented in a narrative format.





Results

Preclinical AD model / Author	Key Findings
APP/PS1 Zhai et al., 2025	**Semaglutide** (0.1mg/kg body weight, subcutaneously, biweekly interval for a period of 8 consecutive weeks): ▪ Reduced Aβ accumulation ▪ Improved cognitive performance ▪ Inhibited overactivation of microglia and astrocytes ▪ Decreased proinflammatory mediators and reduced Aβ deposition
P301S Elbadwaye et al., 2025	**Semaglutide** (25 nmol/kg, intraperitoneally every 2 days for 28 days): ▪ Improved spatial learning and memory (Morris Water Maze and Novel Object Location tests, no significant effect in Novel Object Recognition test) ▪ Hindered the abnormal phosphorylation of the tau protein ▪ Reduced hippocampal neurodegeneration ▪ Doubled the levels of the antioxidant marker Nrf2 and reduced microglial activation ▪ Improved glucose tolerance and increased serum GLP-1 levels
3xTg-AD Wang et al., 2024	**Semaglutide** (25 nmol/kg, intraperitoneally every 2 days for 30 days): ▪ Improved working memory and spatial reference memory. ▪ Did not affect general motor activity or exploration ability. ▪ Reduced Aβ deposition in the hippocampal CA1 region (IHC). ▪ Reduced pro-inflammatory cytokines (IL-1β and TNF-α) expression. ▪ Increased anti-inflammatory factors (IL-4 and IL-10) expression.
5XFAD and APP/PS1 Germano et al., 2024	**Semaglutide** (Initial dose of 10 nmol/kg for 1 week, followed by 17 nmol/kg for 1 week, and 25 nmol/kg for subsequent weeks): ▪ Improved novel object recognition in 6-month-old male 5XFAD mice, although semaglutide did not. ▪ No significant effect on amyloid plaque accumulation in the cerebral cortex, hippocampus, or subiculum. ▪ No improvement in neurobehavioral performance. ▪ No significant changes in the density of hippocampal IBA1$^+$ (microglia) or GFAP$^+$ (astrocyte) cells

Study	Population	Primary Endpoint	Secondary Endpoint	Clinical Trial Phase	Duration of Treatment
EVOKE (NCT04777396) [Oral Semaglutide]	▪ Individuals with early AD, ages 55-85, with MCI or mild dementia. **Note:** The design is identical to the EVOKE Plus trial, but without the specific allowance for patients with significant small vessel pathology.	▪ Change in the Clinical Dementia Rating - Sum of Boxes (CDR-SB) score from baseline to week 104.	▪ Change in the Alzheimer's Disease Cooperative Study Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS-ADL-MCI) score, time to progression to CDR global score ≥1.0, change in ADAS-Cog-13 score, change in MoCA score, and change in Alzheimer's Disease Composite Score (ADCOMS)	Phase 3	▪ 156 weeks (104-week main phase + 52-week extension)
EVOKE Plus (NCT04777409) [Oral Semaglutide]	▪ Individuals with early AD, ages 55-85, with MCI or mild dementia. Note: The study allows for participants with a significantly small vessel pathology. Estimated enrollment of 1840.	▪ Change in the Clinical Dementia Rating - Sum of Boxes (CDR-SB) score from baseline to week 104.	▪ Change in the ADCS-ADL-MCI score, time to progression to CDR global score ≥1.0, change in ADAS-Cog-13 score, change in MoCA score, and change in ADCOMS score.	Phase 3	▪ 156 weeks (104-week main phase + 52-week extension)

Conclusion

- Semaglutide has emerged as a **promising therapeutic candidate for Alzheimer's disease** due to its multifaceted mechanism of action targeting key pathological processes. Preclinical investigations have demonstrated that **semaglutide attenuates neuroinflammation, reduces Aβ plaque deposition and restores metabolic homeostasis**—each of which contributes to disease progression.
- These mechanistic insights have provided the rationale for ongoing Phase 3 clinical trials designed to evaluate its efficacy in slowing cognitive and functional decline in affected individuals. If successful, **semaglutide may represent a paradigm shift toward disease-modifying interventions in Alzheimer's disease, rather than symptomatic management alone.**

References

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