

Semaglutide as a Potential Neuroprotective Agent for Neurological and Neurodegenerative Disorders: Mechanisms, Preclinical Evidence, and Translational Challenges and Opportunities

6528

*Rijuta Dhanraj Mukim, Yama Xu, Vito Evola, Mayur S. Parmar

Dr. Kiran C. Patel College of Osteopathic Medicine, Nova Southeastern University, Tampa Bay Regional Campus, Clearwater, Florida, USA

Semaglutide shows neuroprotective effects in preclinical models of Alzheimer’s disease, Parkinson’s disease, stroke, and multiple sclerosis, reducing neuroinflammation, oxidative stress, protein aggregation, and neuronal injury. However, Phase III Alzheimer’s trials showed modest reductions in inflammatory and disease-related biomarkers (e.g., hs-CRP and tau-related markers) without cognitive benefit, indicating that efficacy depends on treatment timing and disease stage.

Introduction

- Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), originally developed for type 2 diabetes and obesity, are increasingly being investigated for neurological applications.
- Semaglutide is a long-acting GLP-1 RA that may influence pathways involved in neurodegeneration, including neuroinflammation, oxidative stress, mitochondrial dysfunction, impaired autophagy, and apoptosis.
- Preclinical and observational findings suggest potential benefits across several central nervous system disorders; however, whether these biological effects translate into meaningful clinical outcomes remains uncertain.
- This review evaluated the mechanistic, preclinical, and clinical evidence supporting semaglutide as a potential neuroprotective and disease-modifying therapy.

Methods

- A narrative review was conducted by synthesizing relevant mechanistic studies, in vitro and animal experiments, observational cohorts, and clinical trials evaluating semaglutide in neurological and neurodegenerative disorders.

Condition	Key Preclinical Effects	Clinical Trial Status & Findings
Alzheimer’s Disease (AD)	↓ Aβ plaques and tau; ↓ neuroinflammation; ↑ cognitive and memory performance	Phase 3 (EVOKE/EVOKE+): Missed primary cognitive endpoints but showed significant positive biomarker changes (e.g., ↓ p-tau, ↓ hsCRP)
Parkinson’s Disease (PD)	↓ Pathological α-synuclein; protects dopaminergic neurons; ↑ motor function	Phase 2: Clinical trials evaluating motor symptoms and disease progression are currently underway
Stroke	↓ Infarct size; inhibits apoptosis; ↑ neurogenesis and functional recovery	Observational: Post-hoc analyses and real-world data show a significant ↓ in first stroke risk
Emerging Areas (MS, IIH, SCI, Mood Disorders)	Broad anti-inflammatory, antioxidant, and behavioral benefits (e.g., ↓ demyelination in MS, ↓ depressive behaviors)	Early Phase / Observational: Pilot trials and cohort data show promising signals, such as reduced intracranial pressure in IIH and improved metabolic factors in SCI

Result

MULTI-TARGET NEUROPROTECTIVE MECHANISMS

THE EVIDENCE HIERARCHY & TRANSLATIONAL GAP

THREE TIERS OF CLINICAL READINESS

- Tier 1: Strongest** Alzheimer’s, Parkinson’s, Stroke (Strong preclinical data)
- Tier 2: Emerging** Multiple Sclerosis, IIH, Psychiatric (Early translational or observational signals)
- Tier 3: Exploratory** Autism, Seizures, Spinal Cord Injury (Primarily preclinical or pilot studies)

THE IMPORTANCE OF THERAPEUTIC TIMING

Early Prevention: Best for early intervention. Observational data suggest greatest benefit.

Late-Stage Symptomatic Treatment: Biological biomarker improvements do not always translate to clinical recovery.

While robust preclinical data exist, the “timing paradox” reveals that biomarker changes may not always lead to clinical recovery in advanced disease stages.

Conclusions

- Semaglutide engages multiple metabolic, inflammatory, and neuroprotective pathways shared across neurological disorders, but robust preclinical findings have not yet translated into established clinical efficacy.
- EVOKE and EVOKE+ results suggest that modifying these pathways after symptomatic Alzheimer’s disease is established may be insufficient to alter disease progression.
- Semaglutide may therefore have greater potential as an earlier preventive intervention in metabolically at-risk populations or as part of combination therapy.
- Future studies should determine the optimal therapeutic window, clarify central versus peripheral mechanisms, improve central nervous system delivery, and evaluate disease-specific dosing in adequately powered randomized clinical trials.

Reference

Contact