

Neuroprotective Potential of GLP-1 Receptor Agonists in Neurodegenerative Diseases: Narrative Review

Potencjał neuroprotekcyny agonistów receptora GLP-1 w chorobach neurodegeneracyjnych: Przegląd narracyjny

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Abstract

Background: Neurodegenerative disorders, particularly Alzheimer's disease (AD) and Parkinson's disease (PD), present substantial global health challenges due to a lack of disease-modifying therapies. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), traditionally used in type 2 diabetes management, have emerged as promising candidates for neuroprotection due to their ability to cross the blood-brain barrier, suppress neuroinflammation, and support neuronal survival.

Objective: This narrative review aims to analyze the clinical efficacy of GLP-1 RAs in mitigating cognitive and motor deficits in patients with AD and PD.

Materials and Methods: A narrative literature review was conducted, encompassing large-scale observational cohort studies, nationwide registry analyses, randomized controlled trials (RCTs), and systematic reviews with meta-analyses evaluating the clinical efficacy and safety of GLP-1 receptor agonists in patients with Alzheimer's disease and Parkinson's disease. Additionally, preclinical in vivo and in vitro evidence was integrated to elucidate the underlying neuroprotective pathways, focusing on brain-derived neurotrophic factor (BDNF) expression, autophagy regulation, neuroinflammation, and blood-brain barrier integrity.

Results: In Alzheimer's disease (AD), observational data associate GLP-1 RA therapy with up to a 63% reduction in dementia risk ($RR = 0.37$) in diabetic populations; however, randomized controlled trials (RCTs) point to cognitive stabilization and metabolic preservation rather than disease reversal. In Parkinson's disease (PD), observational studies suggest a 30% lower risk of disease onset ($HR = 0.70$). Symptomatically, outcomes are highly dependent on drug kinetics: only short-acting formulations (such as exenatide) show statistically significant motor improvements in trials ($MD = -2.93$ on the MDS-UPDRS Part III). Nevertheless, clinical translation remains constrained by high study heterogeneity, short follow-up periods, and a substantial risk of patient dropout due to gastrointestinal side effects.

Conclusions: GLP-1 RAs demonstrate promising neuroprotective properties in preclinical and observational studies, though a clinical dualism exists where motor benefits in PD appear highly dependent on formulation kinetics. However, robust evidence of true disease-modifying efficacy in humans remains to be established through ongoing Phase III clinical trials.

Keywords: glucagon-like peptide-1 receptor agonists; neuroprotection; Alzheimer's disease; Parkinson's disease

Streszczenie

Wprowadzenie: Choroby neurodegeneracyjne, w szczególności choroba Alzheimera (AD) i choroba Parkinsona (PD), stanowią poważne wyzwanie dla zdrowia publicznego na całym świecie z powodu braku leków modyfikujących ich przebieg. Agoniści receptora glukagonopodobnego peptydu 1 (GLP-1 RA), stosowani dotychczas w leczeniu cukrzycy typu 2, okazali się obiecującymi kandydatami do działania neuroprotektoryjnego ze względu na zdolność do przenikania przez barierę krew-mózg, wyciszania stanu zapalnego w układzie nerwowym oraz wspierania przeżywalności neuronów.

Cel: Celem niniejszego przeglądu narracyjnego jest ocena skuteczności klinicznej GLP-1 RA w łagodzeniu deficytów poznawczych i ruchowych u pacjentów z AD i PD.

Materiały i metody: Przeprowadzono przegląd piśmiennictwa o charakterze narracyjnym, obejmujący wielośrodkowe obserwacyjne badania kohortowe, analizy krajowych rejestrów medycznych, badania kliniczne z randomizacją i grupą kontrolną (RCT) oraz przeglądy systematyczne z metaanalizami, oceniające skuteczność kliniczną, bezpieczeństwo stosowania agonistów receptora GLP-1 u pacjentów z chorobą Alzheimera i chorobą Parkinsona. Dodatkowo włączono dowody z przedklinicznych badań *in vivo* oraz *in vitro* w celu naświetlenia leżących u podstaw neuroprotekcji szlaków molekularnych, ze szczególnym uwzględnieniem ekspresji czynnika BDNF, regulacji procesów autofagii, neuroinflamacji oraz integralności bariery krew-mózg.

Wyniki: W chorobie Alzheimera (AD) metaanalizy badań obserwacyjnych wiążą stosowanie GLP-1 RA ze zmniejszeniem ryzyka demencji o nawet 63% ($RR = 0.37$) u pacjentów z cukrzycą. Badania z randomizacją (RCT) wskazują jednak wyłącznie na stabilizację funkcji poznawczych i ochronę metabolizmu komórkowego, a nie na odwrócenie istniejących zmian. W chorobie Parkinsona (PD) dane obserwacyjne wykazują o 30% niższe ryzyko zachorowania ($HR = 0.70$). W leczeniu objawowym PD kluczowa okazuje się kinetyka leku: jedynie preparaty o krótkim czasie działania (np. eksenatyd) przynoszą istotną poprawę motoryczną ($MD = -2.93$ w skali MDS-UPDRS część III). Przełożenie tych wyników na praktykę kliniczną ograniczają jednak: duża niejednorodność badań, krótki czas obserwacji pacjentów oraz wysoki odsetek przerwania leczenia z powodu objawów niepożądanych ze strony przewodu pokarmowego.

Wnioski: Agoniści receptora GLP-1 wykazują obiecujące właściwości neuroprotektoryjne w badaniach przedklinicznych i obserwacyjnych, aczkolwiek w praktyce klinicznej występuje wyraźny dualizm – poprawa funkcji motorycznych w PD jest silnie uzależniona

od właściwości farmakokinetycznych danego leku. Jednoznaczne dowody na rzeczywistą skuteczność modyfikującą przebieg tych chorób u ludzi wymagają potwierdzenia w trwających badaniach klinicznych III fazy.

Słowa kluczowe: agoniści receptora glukagonopodobnego peptydu 1; neuroprotekcja; choroba Alzheimer; choroba Parkinsona.

Introduction

The growing burden of neurodegenerative diseases

Neurodegenerative diseases, particularly Alzheimer's disease (AD) and Parkinson's disease (PD), represent one of the most formidable challenges for modern medicine in the face of global population aging. The number of individuals living with dementia is projected to increase systematically, primarily due to the lack of available disease-modifying therapies that can effectively target underlying pathological mechanisms rather than merely alleviating symptoms [2]. The progressive degradation of neurons leads to an irreversible loss of patient independence, creating an urgent need to search for novel therapeutic strategies [1].

The incretin axis and the brain

The incretin axis, conventionally associated with glucose metabolism, plays a pivotal role in the functioning of the central nervous system (CNS). Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) possess a unique ability to cross the blood-brain barrier, allowing them to interact directly with receptors located on neurons and glial cells. This mechanism involves the suppression of neuroinflammation by reducing microglial activation and lowering the levels of pro-inflammatory cytokines in the brain. Furthermore, GLP-1 agonists protect neurons from oxidative stress and support nerve cell survival, which is crucial for slowing down degenerative processes in brain structures [2].

Aim of the study

The aim of this narrative review is to analyze current scientific evidence (2015–2026) regarding the neuroprotective potential of GLP-1 receptor agonists in neurodegenerative diseases. This article focuses on evaluating the clinical efficacy of these molecules in inhibiting cognitive and motor deficits.

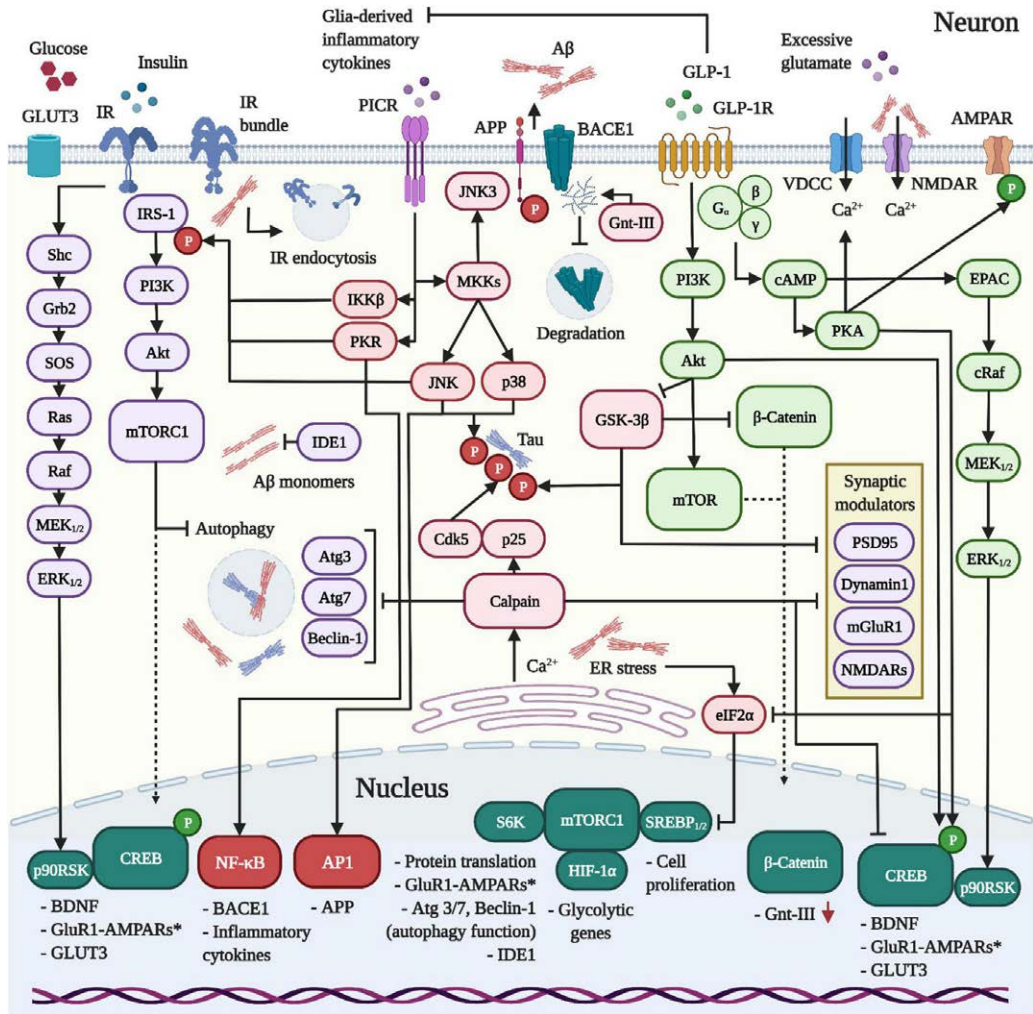


Figure 1. Intracellular neuroprotective signaling pathways of GLP-1 RAs. Reprinted from *Frontiers in Neuroscience* (2022), DOI: 10.3389/fnins.2022.970925, under the Creative Commons Attribution License (CC BY).

As illustrated, the binding of GLP-1 RAs to their specific receptors (GLP-1R) on neurons triggers a cascade of intracellular protective pathways. Key mechanisms include:

PI3K/Akt and MAPK/ERK Activation: These pathways downregulate pro-apoptotic signals while enhancing cellular survival mechanisms and synaptic plasticity.

CREB Pathway and BDNF Expression: The downstream activation of the CREB transcription factor directly upregulates the transcription of brain-derived neurotrophic factor (BDNF), supporting neuronal viability and synaptic maintenance under pathological stress.

Autophagy Regulation: GLP-1R signaling modulates key autophagy markers such as Beclin-1, Atg3, and Atg7. This enhancement of autophagic flux assists in the degradation of toxic protein aggregates, including amyloid-beta (Aβ) and phosphorylated tau, which are key hallmarks of Alzheimer’s disease pathology.

Reduction of Neuroinflammation and ER Stress: By suppressing glial-derived inflammatory cytokines and mitigating endoplasmic reticulum (ER) stress, GLP-1 RAs help preserve blood-brain barrier integrity and prevent excessive calcium influx and glutamate-induced excitotoxicity.

Methodological Rationale and Search Strategy

To ensure a comprehensive retrieval of relevant literature, a structured search was conducted across electronic databases (PubMed, Embase, Web of Science, Cochrane Library; 2015–2026) using key terms related to GLP-1 RAs, neurodegeneration. A narrative review design was applied to enable a broad, multifaceted synthesis encompassing preclinical signaling mechanisms and clinical trial outcomes (RCTs and observational cohorts). Given the methodological heterogeneity across these diverse domains, a structured narrative framework provides the most effective approach to critically analyze the evolving evidence.

Results

Table 1 provides a comprehensive summary of the included clinical trials and observational studies, detailing patient cohorts, interventions, key clinical outcomes, and biological mechanisms of GLP-1 receptor agonists in Alzheimer’s and Parkinson’s diseases.

Table 1. Summary of key clinical trials, systematic reviews, and meta-analyses on GLP-1 RAs in neurodegenerative diseases (2015–2026).

Author & Year	Study Type	Study Population / Cohort Size	Intervention	Main Findings	Limitations
Nørgaard et al. (2022) [1]	Pooled RCTs & nationwide registry cohort	• RCTs: N=15,820 • Registries: N=120,054	GLP-1 RAs (liraglutide, semaglutide) vs. placebo/other antidiabetics	Association with up to a 63% reduction in dementia risk (RR = 0.37) in diabetic populations.	Cohort limited to patients with type 2 diabetes; potential healthy-user bias; observational design.
Yeh et al. (2025) [13]	Propensity score-matched cohort study & meta-analysis	• Large-scale registry database	GLP-1 RAs vs. SGLT2 inhibitors	GLP-1 RAs associated with ~30% lower risk of PD onset (HR = 0.70). However, SGLT2i showed a 20% stronger protective profile.	Retrospective design; potential residual confounding; no direct head-to-head clinical trial validation.

Author & Year	Study Type	Study Population / Cohort Size	Intervention	Main Findings	Limitations
Messak et al. (2025) [4]	Systematic review & meta-analysis of RCTs	• Patients with Parkinson's disease (multiple RCTs)	Various GLP-1 RAs (exenatide, lixisenatide, etc.) vs. placebo	Heterogeneous motor outcomes; high rate of gastrointestinal attrition and risk of mild-to-moderate dehydration.	Small sample sizes in individual trials; short follow-up periods; high dropout rates due to adverse events.
Zhang et al. (2025) [16]	Systematic review & meta-analysis of RCTs	• Parkinson's disease cohorts	Short-acting (e.g., exenatide) vs. long-acting GLP-1 RAs	Statistically significant motor improvement only for short-acting formulations (MD = -2.93 on MDS-UPDRS Part III).	High study heterogeneity; limited long-term data on the durability of the observed motor benefits.
O'Mara et al. (2026) [24]	Meta-analysis of double-blind RCTs	• Non-diabetic patients with MCI or AD	GLP-1 RAs vs. placebo	Cognitive stabilization, preservation of cortical volume, and metabolic protection rather than cognitive reversal.	Phase II exploratory nature of included trials; small sample sizes (N<100 per trial); short study duration (12–18 months).
Badran & Gbreel (2025) [18]	Systematic review & meta-analysis	• Parkinson's disease cohorts	GLP-1 RAs vs. placebo	Confirmed significant risk of muscle mass loss (sarcopenia), worsening of frailty, and acute gallbladder events.	Limited active reporting of sarcopenia across older trial designs; inconsistent monitoring of body composition.

GLP-1 Receptor Agonists in Alzheimer's Disease

The latest clinical data confirm the neuroprotective potential of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in Alzheimer's disease (AD). Large-scale analyses indicate that GLP-1 RA treatment is associated with a significantly lower incidence of dementia in patients with type 2 diabetes, a finding corroborated by nationwide registry data and pooled analyses of clinical trials [1]. Network meta-analyses further demonstrate that GLP-1 RAs offer superior prophylactic benefits compared with selected other antidiabetic agents regarding the overall risk of dementia [3].

A key mechanism observed in AD is the ability of these analogs to improve cerebral glucose metabolism by enhancing glucose transport across the blood-brain barrier, directly counteracting neuronal energy deficits [9-10]. This improvement is reflected in standardized

cognitive assessments, such as the MMSE, and is strongly correlated with the molecular impact of GLP-1 RAs on upregulating brain-derived neurotrophic factor (BDNF) expression. Research shows that restoring neurotrophic support via BDNF promotes synaptic plasticity and neuronal survival even under exposure to toxic amyloid-beta (A β) oligomers, forming the foundation for clinical cognitive improvement [2,6-7,11].

Beyond improving glucose metabolism, GLP-1 modifying factors have been shown to strengthen the blood-brain barrier (BBB) and stimulate progenitor cell proliferation in the subventricular zone [15]. However, clinical translation exhibits a clear disparity between observational data and active trials. Observational cohort analyses and nationwide registries (e.g., [1,14]) suggest that GLP-1 RAs reduce the risk of developing AD by up to 63% (RR = 0.37) compared with control groups. Importantly, these highly promising preventive figures are derived almost exclusively from patients with type 2 diabetes, introducing potential healthy-user bias and confounding by indication. In contrast, double-blind RCTs involving non-diabetic mild cognitive impairment (MCI) or AD cohorts paint a more conservative picture, demonstrating cognitive stabilization (slowing of decline) and preservation of cortical volume (MD = 0.08 mm³, 95% CI: 0.02–0.14, $p = 0.012$) rather than active cognitive restoration [6-7, 24].

GLP-1 Receptor Agonists in Parkinson's Disease

The role of GLP-1 RAs in Parkinson's disease (PD) is currently evaluated from two perspectives: preventive and therapeutic. Recent large-scale population studies suggest that this class exhibits potential in preventing idiopathic PD, reducing the risk of onset by approximately 30% (HR = 0.70, 95% CI: 0.51–0.96, $p = 0.026$) [14]. However, it should be noted that in real-world evidence (RWE) studies, this effectiveness is sometimes lower compared with that of SGLT2 inhibitors, which demonstrate a stronger protective profile in PD prophylaxis (HR = 0.56, 95% CI: 0.44–0.72, $p < 0.001$) [13].

In the context of symptomatic treatment for individuals already diagnosed with the disease, clinical outcomes depend heavily on the drug's pharmacokinetics. A recent meta-analysis revealed that only short-acting formulations (e.g., exenatide) yield a statistically significant improvement in motor function (MD = -2.93 on the MDS-UPDRS Part III, 95% CI: -4.91 to -0.95, $p = 0.004$), whereas long-acting medications fail to show such an effect [16,22]. This is supported by Cochrane review data, indicating that improvements in the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III can exceed the threshold for a minimal clinically important difference (MCID)

and persist even after treatment cessation [17,20]. Nonetheless, the quality of this symptomatic evidence is graded as moderate-to-low due to small sample sizes (typically fewer than 100 participants per trial) and limited follow-up windows (usually 48 to 60 weeks), leaving the longevity of this therapeutic benefit highly uncertain.

Despite promising motor outcomes, GLP-1 agonists do not currently demonstrate a significant impact on non-motor symptoms or the overall quality of life of patients [14,16-18]. The biological rationale for the observed benefits remains the marked increase in BDNF levels (up to 377%) and the protection of dopaminergic neurons from neurotoxicity, as confirmed in preclinical models [2].

Safety and Neuroprotective Mechanisms

While GLP-1 RAs present a promising multi-targeted therapeutic approach, their clinical deployment in neurodegenerative cohorts is constrained by a distinct profile of adverse events. Beyond common, transient gastrointestinal symptoms such as nausea and dyspepsia, clinical trials and post-marketing surveillance highlight several serious systemic risks that require careful consideration in geriatric populations [4-5, 12, 18]. A primary concern in elderly patients is the potential acceleration of skeletal muscle mass loss (sarcopenia) alongside overall weight loss, which can critically compromise physical function and postural stability. Furthermore, gastrointestinal adverse effects—particularly persistent vomiting and diarrhea—frequently lead to acute dehydration, presenting a high risk of prerenal acute kidney injury in vulnerable cohorts. Additionally, therapy with GLP-1 RAs is associated with class-specific risks of acute pancreatitis and gallbladder-related disorders, including cholelithiasis (gallstones) and cholecystitis, necessitating vigilant clinical monitoring and rendering their overall safety profile acceptable only under strict medical supervision [4-5,18].

Discussion

Neuroprotective mechanisms in light of clinical evidence

The analysis of the gathered evidence indicates that GLP-1 receptor agonists (GLP-1 RAs) constitute a therapeutic class with encouraging potential to modulate pathways involved in neurodegenerative disorders. The primary argument supporting their potential is the multi-targeted nature of their molecular action observed in preclinical models. Findings from 2024–2025 suggest that GLP-1 RAs not only improve cerebral glucose metabolism but may also stimulate autophagic processes (through the regulation of Beclin-1 and LC3-II

markers) and increase the expression of BDNF by 76–377% in experimental settings [2,19]. These mechanisms, combined with preclinical evidence of strengthened blood-brain barrier integrity, create a favorable environment that may support neuroprotection [15].

The modulation of autophagic processes is of functional importance, as animal and in vitro models demonstrate that GLP-1 RAs can facilitate the clearance of amyloid-beta and alpha-synuclein aggregates [19]. However, it must be emphasized that such physical clearance of pathological protein aggregates has not yet been directly proven in human clinical trials. At the clinical level, these cellular changes translate primarily to a slowing of symptom progression rather than active neuroregeneration [25].

Dualism of outcomes in Parkinson's and Alzheimer's disease

Throughout the analysis, significant differences in clinical response were observed between the studied disease entities. In Parkinson's disease (PD), the pharmacokinetic properties of the drug emerged as a critical determinant of therapeutic success. Recent meta-analyses indicate that only short-acting formulations (e.g., exenatide) yield statistically significant motor improvements (MD = -2.93, 95% CI: -4.91 to -0.95, $p = 0.004$) [16]. The persistence of these motor benefits beyond the washout period, frequently exceeding the minimal clinically important difference (MCID) threshold, points toward a potential neuroprotective or structural effect rather than a purely transient symptomatic relief, though confirmation in larger cohorts remains necessary [17,22].

Conversely, while GLP-1 RAs demonstrate a robust reduction in dementia risk in Alzheimer's disease cohorts, the clinical picture in Parkinson's disease is far more nuanced. The profound neuroprotection initially observed in animal models often fails to translate into immediate quality-of-life improvements as measured by scales such as the PDQ-39. This discrepancy highlights a major translational barrier (from bench to bedside) and suggests that pharmacological interventions in PD clinical trials may be introduced too late in the disease trajectory, when the remaining neuronal reserve is already insufficient for structural regeneration [15,18].

Comparison with other modern antidiabetic therapies

An important aspect of the discussion is the positioning of GLP-1 RAs relative to other classes, such as SGLT2 inhibitors and DPP4 inhibitors. Although GLP-1 RAs are highly effective in reducing cardiovascular events and stroke, recent network meta-analyses suggest that SGLT2 inhibitors may exhibit higher efficacy in pure Parkinson's disease prophylaxis (HR = 0.56, 95% CI: 0.44–0.72, $p < 0.001$) [13,23]. Furthermore, reports of

a potentially lower risk of developing PD in patients using DPP4 inhibitors (OR = 0.54, 95% CI: 0.38–0.77, $p < 0.001$) compel caution before declaring GLP-1 RAs the sole optimal choice in preventive neurology [23–24].

Safety of therapy and systemic challenges

Despite encouraging clinical signals, integrating GLP-1 RAs into neurological treatment standards faces complex safety and tolerability barriers, particularly within frail, elderly populations. The high frequency of gastrointestinal adverse events (nausea, reflux, chronic vomiting) is not merely a matter of patient discomfort; in geriatric patients, it carries a substantial risk of severe dehydration. For patients with Parkinson's disease, who frequently suffer from autonomic dysfunction and orthostatic hypotension, even mild dehydration can trigger severe hypotensive episodes, increasing the frequency of syncope and subsequent trauma.

Furthermore, the non-selective weight loss induced by GLP-1 RAs often involves a significant reduction in lean skeletal muscle mass rather than exclusively adipose tissue. In patients already suffering from neurodegenerative decline, this muscle wasting directly exacerbates age-related sarcopenia. In Parkinson's disease, loss of muscle strength severely compromises postural stability, accelerating gait impairment and elevating the risk of debilitating falls. In Alzheimer's disease, rapid muscle loss accelerates the onset of physical frailty syndrome, substantially shortening the window of patient independence [18,20].

Clinicians must also account for less frequent but severe class-specific complications. The association of GLP-1 RAs with acute pancreatitis and gallbladder diseases (such as cholelithiasis and acute cholecystitis) requires careful screening. Delayed gallbladder emptying and altered bile composition under GLP-1 therapy can precipitate biliary colic, a condition that may be difficult to diagnose early in cognitively impaired AD patients who cannot communicate symptoms effectively. These concerns, combined with epidemiological signals indicating an elevated risk of thyroid malignancies (OR = 1.58, 95% CI: 1.10–2.27, $p = 0.013$) [23], underscore the necessity of rigorous, individualized patient selection and careful dosage titration rather than a generalized prescribing approach.

Methodological Quality and Limitations of Current Evidence

To objectively assess the clinical viability of GLP-1 RAs in neurology, a critical appraisal of the current literature's quality is mandatory. The existing body of evidence suffers from several methodological vulnerabilities that prevent immediate clinical implementation:

Observational Confounding vs. RCT Efficacy: The dramatic risk reductions reported in dementia prevention (up to 63% [14]) and Parkinson's disease prophylaxis (30% [13]) stem from retrospective, observational cohort studies of patients treated for type 2 diabetes. These studies are inherently susceptible to residual confounding, such as the "healthy-adherer effect" (patients compliant with antidiabetic regimens may engage in healthier lifestyles overall).

Sample Size and Follow-up Constraints: Most double-blind RCTs evaluating symptomatic benefits (especially in PD) are phase II exploratory trials with highly restricted sample sizes (e.g., $N < 100$) and short follow-up durations (typically 12–18 months). Since neurodegenerative progression occurs over decades, these brief observational windows cannot definitively distinguish true disease-modification from transient symptomatic enhancement.

High Attrition Rates: Due to the hallmark gastrointestinal adverse effects of GLP-1 RAs (nausea, vomiting, weight loss), clinical trials report high dropout rates (often exceeding 15–20%). This high attrition introduces attrition bias, potentially skewing efficacy results toward healthier, more tolerant survivors.

Lack of Direct Head-to-Head Comparisons: While network meta-analyses [13,23] attempt to rank GLP-1 RAs against SGLT2 or DPP4 inhibitors, there is a total absence of direct, head-to-head RCTs comparing these metabolic agents in neurodegenerative cohorts. Consequently, the relative superiority of GLP-1 RAs remains statistical rather than clinically validated.

Consequently, according to the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) guidelines, the quality of evidence supporting the preventive neurological benefits of GLP-1 RAs is considered moderate, while the evidence supporting active motor and cognitive symptom modification remains low-to-moderate. Large-scale, multicenter Phase III trials with multiyear follow-ups are urgently required to upgrade these recommendations.

Limitations of the Study

While this review provides valuable insights into the neuroprotective potential of GLP-1 RAs, several key limitations of the current literature must be acknowledged:

Observational Bias and Confounding: High risk-reduction estimates (up to 63% in dementia and 30% in Parkinson's disease) stem mostly from observational studies in

diabetic cohorts. These findings are vulnerable to residual confounding, indication bias, and the healthy-user effect.

Sample Size and Duration Constraints: Most randomized controlled trials (RCTs) are phase II exploratory studies with small cohorts (fewer than 100 participants per arm) and short follow-up windows (12–18 months). This duration is insufficient to prove true, long-term disease modification versus transient symptomatic relief.

High Attrition Rates: The frequent occurrence of gastrointestinal adverse effects led to significant patient dropout rates across trials, introducing potential attrition and survivor bias.

Lack of Direct Comparative Evidence: There is a total absence of head-to-head clinical trials comparing GLP-1 RAs with other metabolic therapies (e.g., SGLT2 or DPP4 inhibitors), preventing firm conclusions regarding absolute pharmacological superiority.

Conclusion

The scientific and clinical evidence analyzed in this review suggests that glucagon-like peptide-1 receptor agonists (GLP-1 RAs) represent a highly interesting therapeutic class with promising neuroprotective properties. Their capacity to cross the blood-brain barrier appears to trigger multi-targeted cascades in experimental models, including the upregulation of BDNF expression (by 76–377%) and the modulation of autophagy markers (Beclin-1, LC3-II). While these preclinical pathways facilitate the reduction of toxic protein aggregates (such as amyloid-beta and alpha-synuclein) in vitro and in vivo, further research is strictly required to verify whether these clearance mechanisms occur at a clinically meaningful level in human patients.

Clinical data highlight a distinct dualism in therapeutic response depending on the specific disease pathology and the pharmacokinetic profile of the administered molecule. In Alzheimer's disease, observational studies in diabetic populations show a lower incidence of dementia (RR = 0.37), but randomized controlled trials in non-diabetic cohorts point toward cognitive stabilization and the preservation of brain volume rather than active cognitive restoration. In Parkinson's disease, clinical benefits appear highly sensitive to drug kinetics; only short-acting agents (e.g., exenatide) have achieved statistically significant improvements in motor scores on the MDS-UPDRS Part III (MD = -2.93), whereas long-acting formulations have yet to demonstrate comparable clinical efficacy.

However, the transition of GLP-1 RAs from diabetes management to standard neurological practice is constrained by notable safety barriers and translational limitations. Frequent

gastrointestinal adverse events and the risk of weight loss require vigilant monitoring in elderly patients to avoid worsening frailty syndrome. Additionally, potential safety signals, such as the reported association with thyroid malignancies (OR = 1.58), necessitate cautious patient selection. Definitive clinical recommendations await the results of large-scale, multicenter Phase III trials that can objectively establish whether GLP-1 RAs possess true disease-modifying efficacy in human neurodegeneration.

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References

1. Nørgaard CH, Friedrich S, Hansen CT, Gerds T, Ballard C, Møller DV, Knudsen LB, Kvist K, Zinman B, Holm E, Torp-Pedersen C, Mørch LS. 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 Feb 23;8(1):e12268. doi: 10.1002/trc2.12268. PMID: 35229024; PMCID: PMC8864443.
2. Grieco M, Giorgi A, Gentile MC, d'Erme M, Morano S, Maras B, Filardi T. Glucagon-Like Peptide-1: A Focus on Neurodegenerative Diseases. *Front Neurosci*. 2019 Oct 18;13:1112. doi: 10.3389/fnins.2019.01112. PMID: 31680842; PMCID: PMC6813233.
3. Tseng PT, Zeng BY, Hsu CW, Hung CM, Carvalho AF, Stubbs B, Chen YW, Chen TY, Lei WT, Chen JJ, Su KP, Shiue YL, Liang CS. The pharmacodynamics-based prophylactic benefits of GLP-1 receptor agonists and SGLT2 inhibitors on neurodegenerative diseases: evidence from a network meta-analysis. *BMC Med*. 2025 Apr 7;23(1):197. doi: 10.1186/s12916-025-04018-w. PMID: 40189519; PMCID: PMC11974209.
4. Messak M, Abdelmageed A, Senbel AA, Khattab YA, Mandour Y, Shaker O, Rehan AH, Oransa S, Nasr M, Shabeeb AE, Rezq Z, Hossam F, Abouelmagd ME. Efficacy and safety of GLP-1 agonists in Parkinson's disease: a systematic review and meta-analysis of randomized controlled trials. *Naunyn-Schmiedeberg's Arch Pharmacol*. 2025 Aug;398(8):9721-9736. doi: 10.1007/s00210-025-03932-3. Epub 2025 Mar 11. PMID: 40067438; PMCID: PMC12350457.

5. Nogueira LOS, Mazetto RASV, Defante MLR, Antunes VLJ, Gonçalves OR, Corso AMS, Coletta MVD, Boone DL, Machado Filho WS, Borges V, Ferraz HB. Efficacy and safety of glucagon-like peptide 1 agonists for Parkinson's disease: a systematic review and meta-analysis. *Arq Neuropsiquiatr*. 2025 Apr;83(4):1-10. doi: 10.1055/s-0045-1806824. Epub 2025 Apr 27. PMID: 40288416; PMCID: PMC12034413.
6. Bi Z, Wang L, Wang W. Evaluating the effects of glucagon-like peptide-1 receptor agonists on cognitive function in Alzheimer's disease: A systematic review and meta-analysis. *Adv Clin Exp Med*. 2023 Nov;32(11):1223-1231. doi: 10.17219/acem/161734. PMID: 37077141.
7. Ballum H, Dri C, Liao S, Yu M, Le GH, Wong S, Teopiz KM, Kwan ATH, Ho R, Choi H, Rosenblat JD, Vinberg M, K Y Lo H, McIntyre RS. The effect of glucagon-like peptide 1 (GLP-1) receptor agonists on cognition: A systematic review of systematic reviews and meta-analyses. *J Affect Disord*. 2026 Jun 1;402:121310. doi: 10.1016/j.jad.2026.121310. Epub 2026 Jan 30. PMID: 41621451.
8. Abou Elezz AM, Khalefa K, Gadelmawla AF, Khattab YA, Abo Zeid M. Antidiabetic drugs in Parkinson's disease: a comprehensive meta-analysis on efficacy and safety with trial sequential analysis and GRADE evaluation. *Inflammopharmacology*. 2025 Aug;33(8):4577-4593. doi: 10.1007/s10787-025-01873-0. Epub 2025 Aug 5. PMID: 40762930; PMCID: PMC12397177.
9. Tseng PT, Zeng BY, Hsu CW, Hung CM, Carvalho AF, Stubbs B, Chen YW, Chen TY, Lei WT, Chen JJ, Su KP, Shiue YL, Liang CS. The pharmacodynamics-based prophylactic benefits of GLP-1 receptor agonists and SGLT2 inhibitors on neurodegenerative diseases: evidence from a network meta-analysis. *BMC Med*. 2025 Apr 7;23(1):197. doi: 10.1186/s12916-025-04018-w. PMID: 40189519; PMCID: PMC11974209.
10. Laurindo LF, Barbalho SM, Guiguer EL, da Silva Soares de Souza M, de Souza GA, Fidalgo TM, Araújo AC, de Souza Gonzaga HF, de Bortoli Teixeira D, de Oliveira Silva Ullmann T, Sloan KP, Sloan LA. GLP-1a: Going beyond Traditional Use. *Int J Mol Sci*. 2022 Jan 10;23(2):739. doi: 10.3390/ijms23020739. PMID: 35054924; PMCID: PMC8775408.
11. Xu T, Zheng YJ, Wong S, Dri CE, Zhou XT, Teopiz KM, Le GH, McIntyre RS. Molecular evidence associating GLP-1 receptor agonists and brain-derived neurotrophic factors in neurodegenerative and psychiatric disorders: A systematic review. *Asian J Psychiatr*. 2026 Mar;117:104870. doi: 10.1016/j.ajp.2026.104870. Epub 2026 Jan 29. PMID: 41619567.
12. Luo Y, Xia Y, Gong X, Hao M, Wei Q, Liao L. GLP-1 receptor agonists in eye disease: a comprehensive review of current research and future potential. *BMC Ophthalmol*. 2026 Jan 8;26(1):12. doi: 10.1186/s12886-025-04559-x. PMID: 41501669; PMCID: PMC12781364.
13. Yeh JA, Lin SM, Liu YC, Hsu JZ, Huang AH, Munir KM, Peng CC, Loh CH, Huang HK. Association of SGLT2 inhibitors and GLP-1 receptor agonists with the risk of Parkinson's disease in patients with type 2 diabetes: A propensity score-matched cohort study with meta-analysis. *Diabetes Res Clin Pract*. 2025 Nov;229:112914. doi: 10.1016/j.diabres.2025.112914. Epub 2025 Sep 19. PMID: 40976497.
14. Choudhury I, Ward JH, Mahesh S, Alam U, Azmi S, Anson M. Effect of Glucagon-Like-Peptide-1 Receptor Agonists (GLP-1 RA) on Neuropsychiatric Outcomes: A Systematic Review and Meta-Analysis. *Clin Ther*. 2026 Apr;48(4):347-384. doi: 10.1016/j.clinthera.2026.02.010. Epub 2026 Mar 19. PMID: 41862354.
15. Erbil D, Eren CY, Demirel C, Küçüker MU, Solaroğlu I, Eser HY. GLP-1's role in neuroprotection: a systematic review. *Brain Inj*. 2019;33(6):734-819. doi: 10.1080/02699052.2019.1587000. Epub 2019 Apr 2. PMID: 30938196.

16. Zhang Y, Wang C, Wang Y, Wang T. Clinical efficacy of GLP-1 receptor agonists in the treatment of Parkinson's disease: a systematic review and meta-analysis of randomized controlled trials. *J Neurol*. 2025 Aug 4;272(9):555. doi: 10.1007/s00415-025-13301-y. PMID: 40760123.
17. Mulvaney CA, Duarte GS, Handley J, Evans DJ, Menon S, Wyse R, Emsley HC. GLP-1 receptor agonists for Parkinson's disease. *Cochrane Database Syst Rev*. 2020 Jul 23;7(7):CD012990. doi: 10.1002/14651858.CD012990.pub2. PMID: 32700772; PMCID: PMC7390475.
18. Badran AS, Gbreel MI. From diabetes to dopamine: Evaluating the disease-modifying potential of GLP-1 receptor agonists in Parkinson's disease. A systematic review and meta-analysis of placebo-controlled trials. *Neurol Sci*. 2025 Nov;46(11):5643-5655. doi: 10.1007/s10072-025-08411-4. Epub 2025 Aug 21. PMID: 40835782.
19. Sioufi MC, Heroiu I, Wong S, Le GH, Dri CE, Zheng YJ, Teopiz KM, Rhee TG, Lo HKY, Guillen-Burgos HF, McIntyre RS. The effect of GLP-1 receptor agonists on autophagy: insights gathered from research evaluating neurodegenerative disorders with these agents. *Acta Neuropsychiatr*. 2026 Feb 13;38:e24. doi: 10.1017/neu.2026.10060. PMID: 41684077.
20. Helal MM, AbouShawareb H, Abbas OH, Haddad R, Zain Y, Osman ASA, Hassan AK. GLP-1 receptor agonists in Parkinson's disease: an updated comprehensive systematic review with meta-analysis. *Diabetol Metab Syndr*. 2025 Aug 23;17(1):352. doi: 10.1186/s13098-025-01888-1. PMID: 40849485; PMCID: PMC12374370.
21. Albuquerque MB, Nunes LEDB, Oliveira Maldonado JV, Melo Ferreira DG, Margato MM, Rabelo LV, Valença MM, Oliveira Cordeiro LH. GLP-1 receptor agonists for Parkinson's disease: An updated meta-analysis. *Parkinsonism Relat Disord*. 2025 Jan;130:107220. doi: 10.1016/j.parkreldis.2024.107220. Epub 2024 Nov 29. PMID: 39642803.
22. Wang SY, Wu SL, Chen TC, Chuang CS. Antidiabetic Agents for Treatment of Parkinson's Disease: A Meta-Analysis. *Int J Environ Res Public Health*. 2020 Jul 3;17(13):4805. doi: 10.3390/ijerph17134805. PMID: 32635358; PMCID: PMC7369739.
23. Tang H, Zhang B, Lu Y, Donahoo WT, Singh Ospina N, Kotecha P, Lu Y, Tong J, Smith SM, Rosenberg EI, Kimmel SE, Bian J, Guo J, Chen Y. Assessing the benefit-risk profile of newer glucose-lowering drugs: A systematic review and network meta-analysis of randomized outcome trials. *Diabetes Obes Metab*. 2025 Mar;27(3):1444-1455. doi: 10.1111/dom.16147. Epub 2024 Dec 26. PMID: 39723481; PMCID: PMC12135018.
24. O'Mara A, Mody BP, Mammi M, Simjian T, Ghattas K, Kaliki S, Le NPM, Liew A, Migliore M, Mekary RA. The effect of GLP-1 receptor agonists on cognition in nondiabetic patients with mild cognitive impairment or alzheimer's disease: a meta-analysis of randomized controlled trials. *Neurol Sci*. 2026 Jan 12;47(1):149. doi: 10.1007/s10072-025-08602-z. PMID: 41524953.
25. Leta V, Ray Chaudhuri K, Milner O, Chung-Faye G, Metta V, Pariante CM, Borsini A. Neurogenic and anti-inflammatory effects of probiotics in Parkinson's disease: A systematic review of preclinical and clinical evidence. *Brain Behav Immun*. 2021 Nov;98:59-73. doi: 10.1016/j.bbi.2021.07.026. Epub 2021 Aug 5. PMID: 34364965.