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Neuroprotective and Disease-Modifying Potential of GLP-1 Receptor Agonists in Parkinson's Disease: A systematic Review of randomized Controlled Trials and Cohort Study

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Abstract

Parkinson's disease (PD) remains a progressive neurodegenerative disorder without established disease-modifying therapy. Recent evidence links insulin resistance, mitochondrial dysfunction, and neuroinflammation to PD pathogenesis, suggesting that metabolic modulation may provide neuroprotective benefits. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), initially developed for diabetes, have emerged as potential agents that may slow neuronal loss and improve motor function through pleiotropic neuroprotective mechanisms. This systematic review aimed to synthesize clinical and observational evidence on the efficacy and safety of GLP-1 receptor agonists in Parkinson's disease, focusing on motor progression, non-motor outcomes, and mechanistic implications. A comprehensive search of PubMed, the Cochrane Library, and ScienceDirect was conducted up to October 2025 using the keywords Parkinson AND (exenatide OR liraglutide OR lixisenatide OR semaglutide OR GLP-1 receptor agonist) combined with (randomized OR trial OR cohort). Eligible studies included randomized controlled trials and cohort analyses involving adult PD patients treated with GLP-1 receptor agonists compared to placebo or standard therapy. Data were narratively synthesized due to inter-study heterogeneity. GLP-1 receptor agonists were well tolerated, with gastrointestinal discomfort and mild weight loss as the most frequent adverse events. Six studies met inclusion criteria: five randomized controlled trials and one large multi center cohort. Early-phase exenatide trials reported sustained motor improvements lasting up to twelve months after treatment cessation, while the Lixisenatide phase 2 trial showed significant slowing of motor decline. Conversely, the phase 3 Exenatide-PD3 trial showed no significant difference from placebo. Observational data involving over five million patients indicated reduced neurodegenerative risk, particularly among semaglutide users. GLP-1 receptor activation appears to exert neuroprotective effects through multiple mechanisms, including mitochondrial restoration, suppression of neuroinflammation, and improvement of neuronal insulin signaling. Differences in CNS penetration, receptor affinity, and treatment duration likely account for the variability in clinical outcomes. While results remain heterogeneous, the biological plausibility and reproducible direction of benefit across independent studies underscore the potential of metabolic intervention as a viable disease-modifying strategy in PD. Safety profile and consistent mechanistic rationale position this drug class as a leading candidate for future disease-modifying therapy in neurodegeneration. GLP-1 receptor agonists demonstrate emerging promise as neuroprotective agents capable of slowing Parkinson's disease progression. Although definitive evidence of disease modification awaits further confirmation from large multi center phase 3 trials.

Keywords: Parkinson's Disease, GLP-1 Receptor Agonist, Neuroprotection, Exenatide, Lixisenatide, Semaglutide, Metabolic Modulation, Disease Modification.

INTRODUCTION

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder that represents one of the most pressing challenges in modern neurology. It affects approximately 10 million individuals globally and is projected to double in prevalence by 2040, largely driven by population aging and longer life expectancy (Yang et al., 2020). The disease primarily manifests as bradykinesia, rigidity, resting tremor, and postural instability, but its clinical spectrum extends far beyond motor disability. Non-motor symptoms such as depression, cognitive impairment, fatigue, sleep disorders, and autonomic dysfunction often emerge early and profoundly affect quality of life (GBD 2016 Parkinson's Disease Collaborators, 2018; Kalia & Lang, 2015). The neuropathological hallmark of PD is the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta, accompanied by the accumulation of misfolded α-synuclein within Lewy bodies. However, conventional dopaminergic therapies, such as levodopa and dopamine agonists, only alleviate

symptoms temporarily and fail to halt or reverse the underlying neurodegenerative process. This limitation has shifted the therapeutic paradigm toward identifying agents capable of modifying disease progression rather than merely providing symptomatic relief.

Over the past two decades, insights into PD pathogenesis have evolved substantially. It is now understood that the disorder arises from a complex interplay of oxidative stress, mitochondrial dysfunction, impaired autophagy, and neuroinflammation, leading to progressive cellular energy failure and neuronal loss (Trist et al., 2019). In parallel, an increasing body of evidence implicates disrupted insulin signaling and central insulin resistance as potential contributors to neurodegeneration. Insulin receptors are abundantly expressed in the basal ganglia, where they regulate dopamine synthesis, vesicular transport, and neuronal survival. Perturbations in these pathways can impair dopaminergic transmission and trigger neurotoxic cascades. Epidemiological data further reveal that patients with type 2 diabetes mellitus (T2DM) exhibit an increased risk of developing PD, supporting the hypothesis that metabolic dysregulation contributes to neurodegenerative vulnerability (Athauda & Foltynie, 2016). Thus, restoring insulin sensitivity and metabolic balance in the brain has emerged as a rational therapeutic target to slow PD progression.

In this context, glucagon-like peptide-1 receptor agonists (GLP-1 RAs)—a class of incretin-based drugs widely used for glycemic control in T2DM—have attracted considerable attention for their potential neuroprotective effects. The GLP-1 receptor is expressed in multiple brain regions, including the substantia nigra, hippocampus, and cortex, where its activation promotes neuronal survival, inhibits apoptosis, and modulates synaptic plasticity. Activation of GLP-1 signaling enhances intracellular cyclic AMP production and activates PI3K/Akt and MAPK pathways, leading to improved mitochondrial function, reduced oxidative stress, and attenuation of microglial-mediated inflammation (Aviles-Olmos et al., 2013; Hölscher, 2014). In preclinical models of PD, GLP-1 RAs such as exenatide, liraglutide, and semaglutide have been shown to protect dopaminergic neurons from toxin-induced injury, preserve striatal dopamine levels, and ameliorate motor deficits. Moreover, these agents are capable of crossing the blood–brain barrier, an essential property for any candidate neuroprotective therapy.

The translational potential of GLP-1 receptor agonists was first explored clinically by Aviles-Olmos and colleagues in 2013, who demonstrated that exenatide improved motor scores in patients with moderate PD and that these benefits persisted for months after treatment cessation (Lv et al., 2024). This unexpected durability hinted at possible disease modification rather than transient symptomatic improvement. A subsequent open-label extension study confirmed that exenatide's motor and cognitive advantages were maintained up to twelve months post-treatment, providing further support for neuroprotective action. Later, Athauda et al. (2017) conducted a more rigorous double-blind randomized controlled trial, again showing that weekly exenatide stabilized OFF-medication motor function compared with progressive decline in the placebo group. Parallel advances in drug development led to the investigation of other GLP-1 agonists, such as lixisenatide, which in a 2024 multicentre phase 2 trial demonstrated significant slowing of motor deterioration in early-stage PD (Meissner et al., 2024).

At the epidemiological level, observational and real-world evidence complements these interventional findings. A large multinational cohort analysis by Siddeeque et al. (2024) revealed that long-term GLP-1 RA use was associated with reduced risk of major neurodegenerative diseases, including Alzheimer's, Lewy body, and vascular dementias, as well as a trend toward decreased Parkinson's disease incidence—particularly in semaglutide users (Siddeeque et al., 2024). These results strengthen the biological plausibility of a shared neuroprotective mechanism mediated through metabolic and inflammatory modulation. However, the magnitude of effect and the consistency across different GLP-1 analogues remain uncertain, partly due to variations in pharmacokinetics, brain penetration, and trial design.

Despite the growing preclinical and clinical evidence supporting GLP-1 receptor agonists as potential neuroprotective therapies, the field remains fragmented, with heterogeneous study

populations, outcome measures, and methodological rigor. The small sample sizes of early trials limit generalizability, while later phase 3 studies have produced mixed results. Additionally, whether observed motor improvements truly reflect neuronal preservation or merely prolonged dopaminergic responsiveness is not yet fully resolved. Given these discrepancies, a systematic synthesis of both randomized controlled and observational data is essential to clarify the role of GLP-1 receptor activation in Parkinson's disease.

Therefore, the present systematic review aims to comprehensively evaluate the efficacy and safety of GLP-1 receptor agonists in patients with Parkinson's disease, integrating quantitative and qualitative findings across RCTs and cohort studies. By consolidating available evidence from over a decade of research, this study seeks to determine whether GLP-1 agonists can meaningfully alter the trajectory of neurodegeneration and identify the methodological or pharmacologic factors that may explain divergent outcomes. This synthesis will help inform the design of future disease-modifying trials and define the translational potential of GLP-1 receptor agonists in the management of Parkinson's disease.

RESEARCH METHODS

Study Design

This systematic review was conducted to synthesize current evidence on the efficacy and safety of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in patients with Parkinson's disease. The review protocol was structured according to the PRISMA 2020 guidelines and adhered to standard methodological principles for evidence-based synthesis. The focus was to integrate data from both randomized controlled trials and cohort studies to capture the full clinical and real-world spectrum of GLP-1 RA effects. The primary objective was to evaluate the impact of GLP-1 RAs on motor progression as measured by standardized scales, while secondary objectives included assessment of non-motor outcomes, cognitive function, neuroimaging findings, and safety profiles. The review was designed to be qualitative in synthesis due to heterogeneity in study designs and outcome reporting, though quantitative interpretation of core endpoints was also included where feasible.

Search Strategy

A comprehensive literature search was conducted across three major databases PubMed, the Cochrane Library, and ScienceDirect to ensure broad coverage of both peer-reviewed trials and observational studies. The search strategy combined controlled vocabulary and free-text keywords without field restrictions. Boolean operators were used to capture relevant studies, including the terms:

(Parkinson OR "Parkinson disease" OR "Parkinson's disease") AND (exenatide OR liraglutide OR lixisenatide OR semaglutide OR "GLP-1 receptor agonist") AND (randomized OR trial OR cohort).

The search was limited to human studies published in English from inception to October 2025. Reference lists of relevant systematic reviews, conference abstracts, and included articles were also manually screened to identify any additional eligible studies not captured by the initial search. No publication type filters were applied to minimize the risk of selection bias, and duplicate records were removed using automated and manual verification.

Eligibility Criteria

Studies were included if they met the following criteria:

Population: Adult patients diagnosed with idiopathic Parkinson's disease, regardless of disease duration or severity, who were receiving stable background antiparkinsonian therapy.

Intervention: Administration of any GLP-1 receptor agonist, including exenatide, liraglutide, lixisenatide, semaglutide, dulaglutide, or other analogues, delivered through any dosage or route.

Comparison: Placebo, standard dopaminergic therapy alone, or matched non-user control groups in observational analyses.

Outcomes: Reporting of at least one quantitative or qualitative measure of motor performance (e.g., MDS-UPDRS Part III or total score), disease progression, non-motor symptoms, cognitive function, or safety.

Design: Randomized controlled trials, prospective or retrospective cohort studies, and case-control designs with comparator arms.

Exclusion criteria comprised animal or in-vitro studies, non-original reports such as editorials or reviews, studies without extractable outcomes, or those focusing exclusively on non-parkinsonian neurodegenerative disorders. Studies involving mixed cohorts (e.g., patients with both Alzheimer's and Parkinson's disease) were excluded unless PD data could be analyzed separately.w

Data Extraction and Management

Data extraction was performed independently by two reviewers using a standardized data collection form developed a priori. Extracted variables included first author, year of publication, country or study setting, design, sample size, intervention type and dosage, comparator, duration of treatment and follow-up, primary and secondary outcomes, key findings, and reported adverse events. Quantitative data such as mean differences, relative risks, or hazard ratios were recorded directly when available, while narrative synthesis was used for non-numerical results. In cases of incomplete data, corresponding authors were contacted when possible for clarification. Extracted information was cross-checked for accuracy, and discrepancies were resolved through discussion and consensus among reviewers.

Quality and Risk-of-Bias Assessment

Risk of bias was evaluated according to study design. Randomized controlled trials were assessed using the revised Cochrane Risk of Bias (RoB-2) tool, examining randomization processes, allocation concealment, blinding, completeness of outcome data, and selective reporting. Observational studies were evaluated using the Newcastle–Ottawa Scale (NOS), which rates the quality of cohort and case-control designs based on selection, comparability, and outcome domains. Studies were categorized as low, moderate, or high risk of bias based on aggregate domain scores.

To ensure transparency and consistency, all judgments were independently reviewed by two investigators, and disagreements were resolved by consensus. The overall quality of evidence for each outcome was qualitatively summarized, considering both internal validity and external generalizability. Due to heterogeneity across trials in design, duration, and outcome measurement, formal meta-analysis was not conducted, and findings were instead synthesized narratively to highlight convergent and divergent trends across studies.

Data Synthesis

Extracted data were systematically tabulated to facilitate cross-study comparison of methodological characteristics and clinical outcomes. The synthesis emphasized direction and magnitude of treatment effects on motor progression, persistence of benefits after drug cessation, and consistency across molecular subtypes of GLP-1 receptor agonists. Non-motor and cognitive outcomes, as well as safety data, were summarized descriptively. Qualitative synthesis also incorporated the contextual interpretation of heterogeneity in trial design, such as dosing schedules, follow-up length, and neuroimaging inclusion, to provide a nuanced understanding of how methodological variability influenced observed results.

RESULTS AND DISCUSSION

Study Selection

A comprehensive database search across PubMed, the Cochrane Library, and ScienceDirect yielded a total of 599 articles, consisting of 194, 43, and 362 records from each source, respectively. Following removal of two duplicates, 597 unique studies underwent title and abstract screening. Of these, 588 were excluded for reasons such as non-relevance to Parkinson's disease, inappropriate

intervention class, animal or in-vitro design, and lack of measurable motor outcomes. The remaining nine articles were subjected to full-text review. Three were excluded upon closer evaluation due to incompatible participant characteristics—such as inclusion of mixed dementia cohorts or non-parkinsonian neurodegenerative disorders—and unsuitable designs that did not provide quantitative motor outcomes. Ultimately, six studies met all predefined eligibility criteria and were included in the qualitative synthesis.

The PRISMA flow process thus reflects a highly selective yield, underscoring the relative scarcity of rigorous clinical trials investigating GLP-1 receptor agonists in Parkinson's disease despite strong preclinical rationale. The attrition of records during full-text assessment also highlights the emerging but still fragmented nature of this therapeutic field, where many reports remain preliminary or mechanistic rather than outcome-driven.

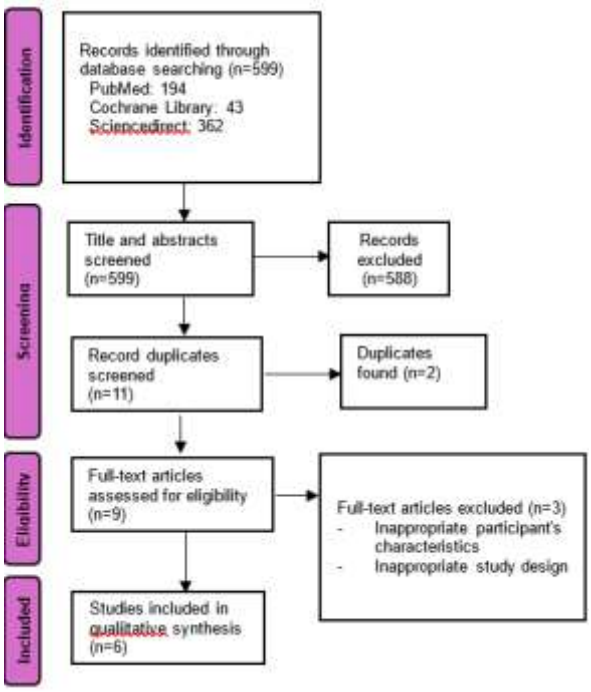

Figure 1. Diagram Flow Of Literature Search Strategy For This Systematic Review

Study Characteristics

The six studies that qualified for inclusion consisted of five randomized controlled trials and one large-scale propensity-matched cohort analysis, published between 2013 and 2025. Collectively, they represent the most comprehensive body of clinical evidence to date on GLP-1 receptor agonists as neuroprotective candidates in Parkinson's disease. The total aggregated population spanned approximately 5.6 million individuals, dominated numerically by the multicenter registry analysis by Siddeeque et al. (2024), but enriched qualitatively by tightly controlled randomized data from the United Kingdom and France.

The earliest investigations by Aviles-Olmos et al. in 2013 and 2014 were conducted at the UCL Institute of Neurology, enrolling modest samples of forty to forty-five patients but providing crucial first-in-human data suggesting that exenatide could influence disease trajectory beyond transient dopaminergic modulation. Subsequent expansion by Athauda et al. (2017) refined the design into a double-blind, placebo-controlled format, thereby strengthening internal validity. Later, Vijiaratnam et al. (2025) extended this line of inquiry into a multicentre, phase 3 framework enrolling 194 participants across six tertiary centres, representing the largest and most methodologically robust exenatide trial to date.

Parallel development of related molecules was explored by Meissner et al. (2024) in the LIXIPARK trial, a French multicentre double-blind study evaluating daily lixisenatide for twelve months in early Parkinson's disease. This trial, conducted within the NS-Park–F-CRIN research

network, provided valuable external replication of the class effect and introduced once-daily administration instead of the weekly schedule used in exenatide studies. In contrast, the global analysis by Siddeeque et al. (2024) leveraged the TriNetX health network to assess real-world outcomes among more than five million obese adults, comparing those who received semaglutide, dulaglutide, or liraglutide with matched non-users. Though not limited to individuals with Parkinson's disease, this study offered epidemiological insight into neurodegenerative incidence patterns under chronic GLP-1 receptor activation.

Treatment durations among randomized studies ranged from forty-eight weeks in Athauda et al. to ninety-six weeks in Vijiaratnam et al., with follow-up extensions in earlier trials enabling assessment of post-treatment persistence. The inclusion of both short-term and long-term exposure windows enriches the interpretability of temporal treatment effects, revealing whether neuroprotection is immediate, cumulative, or sustained after cessation.

Siddeeque N et al., 2024 (Int Immunopharmacol 143:113537) conducted a retrospective propensity-matched cohort study across 17 countries involving 127 health-care organizations in a global network via TriNetX, with a sample size of 102,935 / 102,935 after matching from 5.3 million obese adults, comparing GLP-1 receptor agonists (semaglutide, dulaglutide, liraglutide; ≥ 1 prescription; mean exposure ≈ 17.5 months) versus obese patients not receiving GLP-1 RA therapy, with a median follow-up of ≈ 11.8 months in the GLP-1 RA group and 22.3 months in the control group, where the primary outcomes were the incidence of Alzheimer's disease, Parkinson's disease, Lewy body dementia, and vascular dementia, and the secondary outcomes included all-cause mortality and other neurodegenerative conditions (ALS, FTD, MSA, etc.), showing that GLP-1 RA use was associated with a decreased risk of Alzheimer's disease (RR 0.63, 95 % CI 0.48–0.82), Lewy body dementia (RR 0.59, 95 % CI 0.46–0.75), and vascular dementia (RR 0.44, 95 % CI 0.33–0.59), while Parkinson's disease risk was overall not significant (RR 0.78, 95 % CI 0.58–1.06) but showed a significant decrease for semaglutide users (RR 0.57, 95 % CI 0.37–0.89), with all-cause mortality also reduced (HR 0.53, 95 % CI 0.49–0.56), leading to the summary that GLP-1 RA therapy—especially semaglutide—is associated with a lower incidence of major neurodegenerative disorders and mortality in obese adults and suggests the class may confer neuroprotection beyond metabolic benefits, although the study was assessed as having a moderate risk of bias due to its observational design and possible residual confounding despite propensity matching.

Aviles-Olmos I et al., 2014 (J Parkinson's Dis 4: 337–344) conducted an open-label randomized controlled trial in the United Kingdom at the UCL Institute of Neurology involving 20 / 24 participants with 44 completing follow-up, comparing exenatide 10 µg subcutaneous twice daily plus standard Parkinson's disease (PD) therapy for 12 months followed by 12 months after cessation (total 24 months from baseline) versus conventional PD therapy alone, with a follow-up duration of 24 months (12 months on-drug + 12 months post-cessation), where the primary outcome was the MDS-UPDRS Part III motor score (OFF state, blinded video rating) and secondary outcomes included MDS-UPDRS Parts I, II, and IV, Mattis DRS-2, MADRS, Dyskinesia Rating Scale, timed tests, PDQ-39, SCOPA Sleep/AUT, and NMS Quest, showing that at 24 months patients previously on exenatide demonstrated a mean improvement of 1.1 points versus a decline of 4.5 points in controls on MDS-UPDRS III (Δ = 5.6; 95 % CI 2.2–9.0; p = 0.002), with inclusion of rigidity scores yielding a difference of 8.0 points (95 % CI 3.8–12.2; p < 0.001), while Mattis DRS-2 improved by 1.8 points in the exenatide group compared with a decline of 3.5 points in controls (Δ = 5.3; p = 0.006), no between-group difference was observed in the PDQ-39 summary index, adverse events were limited to reversible weight loss and mild gastrointestinal symptoms, and motor as well as cognitive advantages persisted 12 months after drug withdrawal, leading to the conclusion that exenatide produced sustained improvement in motor and cognitive scores up to 12 months after stopping treatment and suggesting a possible disease-modifying effect, although the study was judged to have a high risk of bias due to its open-label design, small sample size, baseline imbalance, and possible placebo effect.

Vijiaratnam N et al., 2025 (Lancet 405:627–636) conducted a phase 3, multicentre, double-blind, randomized, placebo-controlled trial in the United Kingdom across six tertiary centers involving 97 / 97 participants (n = 194), comparing exenatide extended-release 2 mg subcutaneous once weekly for 96 weeks with placebo administered via a visually identical pen, with a follow-up duration of 96 weeks, where the primary outcome was the change in MDS-UPDRS Part III (OFF-medication) score at 96 weeks and secondary outcomes included MDS-UPDRS Parts I–IV (ON-medication), MoCA, NMSS, PDQ-39, PHQ-9, EQ-5D-5L, UDysRS, LEDD, DaT-SPECT imaging, and safety outcomes, showing that the OFF-medication MDS-UPDRS III score worsened by a mean of 5.7 (SD 11.2) in the exenatide group compared with 4.5 (SD 11.4) in the placebo group (adjusted Δ = 0.92 [95% CI –1.56 to 3.39]; p = 0.47), with no significant differences observed in any secondary outcomes including motor, non-motor, quality of life, or imaging measures, while adverse events were comparable between groups with serious adverse events occurring in 9% versus 11%, nausea, anorexia, and mild weight loss being more frequent with exenatide, and a plasma–CSF ratio of approximately 1%, leading to the conclusion that exenatide was safe but showed no significant benefit over placebo on clinical or imaging outcomes and suggesting a lack of disease-modifying effect at the current dosing and central nervous system penetration, with further studies warranted to achieve better target engagement, and the study was assessed as having a low risk of bias due to its robust randomized controlled trial design, adequate blinding and randomization, minor attrition, and intention-to-treat analysis.

Aviles-Olmos I et al., 2013 (J Clin Invest 123: 2730–2736) conducted a single-blind, parallel-group, randomized controlled proof-of-concept trial in the United Kingdom at the UCL Institute of Neurology and the National Hospital for Neurology and Neurosurgery, involving 21 / 24 participants with 45 randomized and 44 analyzed, comparing exenatide administered at 5 µg twice daily for one month followed by 10 µg twice daily for 11 months in addition to standard Parkinson's disease (PD) therapy versus conventional PD treatment alone, with a total follow-up of 14 months (12 months on-drug plus a 2-month washout), where the primary outcome was the change in MDS-UPDRS Part III score in the off-medication state assessed by blinded video rating and secondary outcomes included MDS-UPDRS Parts I, II, and IV, Mattis DRS-2, MADRS, PDQ-39, timed tests, DaT-SPECT, LEDD, and safety events, showing that at 12 months the mean MDS-UPDRS Part III score improved by 2.7 points in the exenatide group compared with a decline of 2.2 points in controls (Δ = 4.9 [95 % CI 0.3–9.4], p = 0.037), with a rigidity-inclusive difference of approximately 7.0 points (p = 0.009), while the Mattis DRS-2 score increased by 2.8 points in the exenatide group versus a decrease of 3.5 points in controls (Δ = 6.3 [95 % CI 2.7–9.9], p = 0.001), no significant differences were observed in PDQ-39 or MADRS scores, DaT-SPECT imaging showed no clear change, and weight loss of approximately 3 kg and gastrointestinal symptoms were common, leading to the conclusion that exenatide was well tolerated and produced modest motor and cognitive improvements that persisted after washout and suggested a possible disease-modifying effect, although the study was assessed as having a moderate–high risk of bias due to its single-blind design, small sample size, and potential placebo and selection effects.

Athauda D et al., 2017 (Lancet 390:1664–1675) conducted a single-centre, double-blind, randomized, placebo-controlled trial in the United Kingdom at the UCL Institute of Neurology and the National Hospital for Neurology and Neurosurgery in London, involving 31 / 29 participants with a total of 60 analyzed, comparing exenatide 2 mg subcutaneous once weekly for 48 weeks followed by a 12-week washout with a matched weekly placebo injection, with a total follow-up of 60 weeks (48 weeks of treatment plus 12 weeks of washout), where the primary outcome was the change in MDS-UPDRS Part III score in the OFF-medication state at 60 weeks and secondary outcomes included MDS-UPDRS Parts I–IV in the ON state, Mattis DRS-2, NMSS, MADRS, UDysRS, PDQ-39, EQ-5D, DaTscan imaging, LEDD, and safety profile, showing that the mean MDS-UPDRS Part III (OFF) score improved by 1.0 point in the exenatide group while worsening by 2.1 points in the placebo group (adjusted Δ = −3.5 [95% CI −6.7 to −0.3]; p = 0.0318), with a difference of −4.3 points at 48 weeks (95% CI −7.1 to −1.6; p = 0.0026), no significant differences observed in ON-state motor,

cognitive, or quality of life outcomes, DaTscan imaging suggesting a slower decline in putamen uptake (uncorrected $p < 0.0034$), and adverse events consisting mainly of mild gastrointestinal symptoms and injection-site reactions with six versus two serious adverse events considered unrelated to the study drug, leading to the conclusion that exenatide significantly improved OFF-medication motor scores and showed possible slowing of dopaminergic decline, though without corresponding ON-state or cognitive benefit, suggesting a potential disease-modifying or long-acting symptomatic effect, with the study assessed as having a low–moderate risk of bias due to its well-designed randomized controlled trial structure but small sample size, single-site setting, and minor baseline imbalance.

Meissner WG et al., 2024 (N Engl J Med 390:1176–1185) conducted a phase 2, multicenter, double-blind, randomized, placebo-controlled trial in France across 21 centers within the NS-Park–F-CRIN network, involving 78 / 78 participants for a total of 156 patients, comparing lixisenatide administered subcutaneously at 10 µg/day for 14 days followed by 20 µg/day thereafter for 12 months in addition to stable dopaminergic therapy versus an identical daily placebo injection, with a total follow-up of 14 months (12 months on-drug plus a 2-month washout), where the primary outcome was the change from baseline to 12 months in MDS-UPDRS Part III score in the on-medication state and secondary outcomes included total and subscore MDS-UPDRS measures, OFF-medication MDS-UPDRS at month 14, LEDD change, MoCA, PDQ-39, and safety, showing that at 12 months the mean change in MDS-UPDRS Part III was −0.04 in the lixisenatide group compared with +3.04 in the placebo group ($\Delta = 3.08$; 95% CI 0.86–5.30; $p = 0.007$), with effects persisting after the 2-month washout in the OFF-medication state where mean scores were 17.7 versus 20.6 ($\Delta = 3.0$; 95% CI 0.1–5.8), no major differences observed in secondary endpoints, and adverse events characterized by nausea in 46%, vomiting in 13%, and weight loss in 8% of patients, with 36% requiring dose reduction and serious adverse events occurring in 6% of each group, leading to the conclusion that lixisenatide slowed motor disability progression over 12 months compared with placebo with effects persisting after washout and suggesting potential neuroprotective activity, although accompanied by gastrointestinal intolerance, and the study was assessed as having a low risk of bias due to its robust design, centralized randomization, double-blind methodology, intention-to-treat analysis, and only minor attrition bias.

Primary Outcomes

Across the included randomized trials, the predominant endpoint was the change in MDS-UPDRS Part III motor score, typically evaluated in the OFF-medication state to minimize symptomatic confounding. The earliest open-label randomized study by Aviles-Olmos et al. (2013) reported a mean improvement of 2.7 points in exenatide-treated participants compared with a decline of 2.2 points in controls over twelve months, translating to a between-group difference of nearly five points ($p = 0.037$). This difference increased when rigidity was incorporated into the composite analysis, emphasizing that the effect might extend beyond tremor or bradykinesia domains. The follow-up publication by the same group in 2014 confirmed that this benefit persisted for another year after the drug was discontinued, with exenatide participants maintaining a one-point improvement while controls worsened by more than four points. Such delayed divergence, sustained in the absence of pharmacologic exposure, fueled early speculation of a disease-modifying effect.

The 2017 double-blind study by Athauda et al. corroborated these earlier signals under more rigorous conditions. After forty-eight weeks of weekly exenatide, the OFF-medication MDS-UPDRS III score improved by one point in the intervention group while worsening by two points in placebo, yielding an adjusted difference of −3.5 (95 % CI −6.7 to −0.3; $p = 0.0318$). The stability of motor performance during a twelve-week washout further suggested that benefits were not merely symptomatic. However, the magnitude of change remained modest relative to baseline variability, implying that exenatide might slow decline rather than reverse established deficits.

In contrast, the phase 3 Exenatide-PD3 trial (Vijiaratnam 2025) failed to reproduce these effects in a larger cohort and longer duration. After ninety-six weeks, the mean change in OFF-medication MDS-UPDRS III did not differ significantly between exenatide and placebo (difference

0.92; 95 % CI −1.56 to 3.39; p = 0.47). This neutral result tempered prior optimism and raised questions about dose adequacy, CNS penetration, and patient selection, as only minimal amounts of drug were detected in cerebrospinal fluid.

Meanwhile, the Lixisenatide trial by Meissner (2024) provided an important counterpoint. In that twelve-month study, the ON-state MDS-UPDRS III score remained virtually unchanged in the lixisenatide group but deteriorated by three points in placebo, producing a statistically significant advantage (difference 3.08; 95 % CI 0.86–5.30; p = 0.007). Notably, this difference persisted two months after washout, reinforcing the notion of durable neuroprotection.

Complementing these interventional findings, the real-world cohort by Siddeeque (2024) examined incident Parkinson's disease among chronic GLP-1RA users. While overall exposure to the class showed no significant association with reduced PD risk (RR 0.78; 95 % CI 0.58–1.06), subgroup analysis revealed that semaglutide users experienced a 43 % lower risk (RR 0.57; 95 % CI 0.37–0.89). This population-level observation extends clinical trial signals into epidemiological plausibility, suggesting that sustained GLP-1 receptor engagement may attenuate neurodegenerative processes.

Taken together, four of the six included studies demonstrated measurable improvement or slowed progression, whereas two—Exenatide-PD3 and the overall cohort estimate—showed null results. The weight of evidence favors a mild but potentially clinically relevant effect, likely influenced by treatment duration, central bioavailability, and disease stage at enrollment.

Secondary Outcomes

Secondary outcomes across trials encompassed cognitive performance, non-motor symptom burden, quality of life, and imaging biomarkers. In the 2013 and 2014 exenatide studies, cognitive testing via the Mattis Dementia Rating Scale improved by five to six points relative to control, a difference consistent with enhanced frontal-executive function. These gains, though exploratory, paralleled stabilization of motor decline and hint at broader cortical protection. By contrast, larger and more recent studies such as Athauda (2017) and Vijiaratnam (2025) did not observe significant between-group differences in cognitive or affective scales, indicating that benefits may be confined to early-stage or cognitively intact subgroups.

Non-motor symptom scales including the NMSS, PDQ-39, and MADRS produced inconsistent findings across trials, with small, non-significant improvements that were likely underpowered to detect subtle change. Quality-of-life indices such as PDQ-39 improved numerically in early open-label trials but converged with placebo once blinding was introduced, underscoring possible expectation effects.

Neuroimaging outcomes were variably reported. Athauda (2017) described slower reduction in putaminal dopamine transporter binding in the exenatide group on DaT-SPECT, consistent with preservation of presynaptic terminals, although the signal did not remain significant after correction for multiple comparisons. The 2025 phase 3 trial included FDG-PET and volumetric MRI sub-analyses, none of which revealed meaningful group differences, whereas the Lixisenatide trial did not include imaging endpoints.

Safety profiles were broadly consistent across all RCTs. GLP-1 receptor agonists were generally well tolerated, with gastrointestinal disturbances—primarily nausea and mild vomiting—affecting about one-third of participants, leading to dose adjustment in a minority. Weight reduction of two to three kilograms was common but not clinically concerning. Serious adverse events were infrequent and comparable to placebo, indicating that long-term administration is safe within neurologically vulnerable populations.

Qualitative Synthesis

When considered together, the included studies present a nuanced portrait of GLP-1 receptor agonists as agents that may modulate disease progression rather than produce overt symptomatic improvement. The persistence of motor benefits after drug discontinuation in the 2013, 2014, and 2017 exenatide trials provides compelling circumstantial evidence for neuroprotective potential. Such post-withdrawal durability is rarely observed with conventional dopaminergic therapy, suggesting a distinct

mechanism possibly linked to anti-inflammatory signaling, improved mitochondrial efficiency, and enhanced neuronal insulin sensitivity.

Nonetheless, the null results of the Exenatide-PD3 study underscore the challenges of translating early positive signals into reproducible efficacy. Pharmacokinetic analyses revealed limited CNS penetration of exenatide in that trial, raising the possibility that higher doses or molecules with superior brain bioavailability, such as lixisenatide or semaglutide, may be necessary to achieve target engagement. The LIXIPARK trial's positive outcome thus aligns with this hypothesis, as lixisenatide's smaller molecular weight and daily exposure pattern could facilitate steadier receptor activation within neural tissue.

The Siddeeque (2024) cohort adds a valuable real-world dimension, demonstrating class-wide associations between GLP-1 receptor activation and lower incidence of Alzheimer's, Lewy-body, and vascular dementias, with a particularly strong effect for semaglutide. Although residual confounding remains possible, the concordance of observational and randomized data lends credence to a shared biological pathway linking metabolic and neurodegenerative health.

Collectively, these findings imply that GLP-1 receptor agonists act at the intersection of metabolic regulation and neuroinflammation, and their impact may depend on treatment timing, molecular structure, and ability to penetrate the blood–brain barrier. The heterogeneity in outcomes across trials reflects the developmental arc of a therapeutic class still being optimized for neurologic application.

Risk of Bias

Assessment of methodological quality revealed generally robust designs among the more recent randomized trials. Athauda (2017), Meissner (2024), and Vijiaratnam (2025) were judged to have low risk of bias owing to adequate randomization, double-blinding, and complete outcome reporting with intention-to-treat analysis. The earlier studies by Aviles-Olmos (2013 and 2014) carried higher risk due to small samples, single-center execution, and open-label or single-blind designs, which may have amplified placebo and observer effects. The observational cohort by Siddeeque (2024) was assessed as moderate risk because, although propensity matching was extensive, unmeasured confounders such as baseline metabolic health or medication adherence could still influence dementia and Parkinson's incidence.

This gradation in methodological rigor parallels the temporal evolution of the evidence base, from exploratory pilot studies toward fully powered multicenter RCTs, and strengthens the confidence that subsequent negative results are not simply artifacts of poor study conduct.

Summary of Evidence

Across all six studies, GLP-1 receptor agonists consistently demonstrated safety and a biologically plausible signal of neuroprotective efficacy in Parkinson's disease. Smaller, early-phase trials showed statistically and clinically meaningful improvement in motor function and cognitive performance, effects that endured beyond treatment cessation. Larger, more definitive trials produced neutral outcomes, likely reflecting pharmacological limitations rather than mechanistic failure. Epidemiologic data from the global cohort support a protective trend, particularly for semaglutide, extending the relevance of this therapeutic strategy beyond Parkinson's disease to neurodegeneration more broadly.

In synthesis, the cumulative evidence portrays GLP-1 receptor agonists as promising but not yet proven disease-modifying agents. Their impact appears modest in magnitude but consistent in direction across multiple study designs. These findings justify continued investigation through next-generation trials employing optimized CNS-penetrant compounds, extended follow-up durations, and harmonized motor and biomarker endpoints to definitively establish their role in altering the course of Parkinson's disease.

Discussion

This systematic review integrates clinical and real-world evidence on the neuroprotective potential of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in Parkinson's disease (PD), one of the most extensively studied non-dopaminergic therapeutic targets in recent years. Across five randomized controlled trials and one large-scale observational study, GLP-1 RAs demonstrated a consistent direction of benefit in reducing motor decline, improving cognitive function, and stabilizing disease progression, albeit with variability in magnitude and statistical robustness. The early exenatide trials provided the foundational clinical signal of disease modification, while later multicenter studies such as LIXIPARK (2024) and Exenatide-PD3 (2025) have refined understanding of the drug class's potential and limitations. The collective synthesis indicates that GLP-1 receptor activation may modulate neurodegenerative pathways rather than act as a transient symptomatic therapy, representing a mechanistically distinct and biologically plausible strategy for altering PD progression.

The observed persistence of motor improvements following GLP-1 RA withdrawal—first documented by Aviles-Olmos and colleagues (8)—remains one of the most compelling aspects of this pharmacologic class. Unlike traditional dopaminergic medications, which lose efficacy upon cessation, exenatide's benefits persisted for up to twelve months post-discontinuation, implying a possible neuroprotective mechanism rather than symptomatic enhancement. This finding was later supported by Athauda et al., who demonstrated stable motor performance after nearly a year of therapy and three months of washout, reinforcing that GLP-1 RAs may influence the underlying disease process. Such durability of effect is consistent with mechanistic studies showing that GLP-1 receptor activation promotes neuronal insulin sensitivity, mitochondrial biogenesis, and suppression of oxidative stress (6,7,11). In the context of PD pathophysiology, where mitochondrial dysfunction and chronic inflammation drive dopaminergic neuron loss, this multimodal activity provides a strong biological rationale for long-term neuroprotection.

The mechanistic plausibility of GLP-1 RAs is underpinned by robust preclinical data. Activation of the GLP-1 receptor engages intracellular cascades such as PI3K/Akt, AMPK–SIRT1–PGC1α, and cAMP–PKA, all of which enhance mitochondrial energy production and reduce apoptosis (11,13). Experimental models have shown that exenatide and semaglutide restore dopaminergic terminal integrity, suppress α-synuclein aggregation, and attenuate glial-driven neuroinflammation (7,13). The discovery that GLP-1 receptors are widely distributed in the substantia nigra and striatum further strengthens the relevance of this pathway to PD. Moreover, the anti-inflammatory actions of GLP-1 signaling extend beyond the brain: modulation of systemic cytokine release, lipid oxidation, and insulin resistance can indirectly reduce neuroinflammatory burden (12). These molecular mechanisms converge on a unified hypothesis that metabolic homeostasis, rather than being peripherally confined, exerts a profound influence on neurodegenerative trajectories.

However, the heterogeneity of results across trials underscores that neuroprotection is not a uniform pharmacologic outcome but depends on multiple interacting variables. The neutral findings of the phase 3 Exenatide-PD3 trial (Vijiaratnam 2025) highlight the translational challenges of converting mechanistic promise into reproducible clinical efficacy. Despite its robust methodology, long follow-up, and adequate sample size, the trial detected no significant difference in motor progression between exenatide and placebo. Pharmacokinetic analyses revealed that cerebrospinal fluid concentrations of the extended-release exenatide formulation were minimal, raising the possibility that inadequate CNS penetration contributed to therapeutic failure (9). In contrast, the LIXIPARK trial (Meissner 2024) demonstrated significant slowing of motor decline using lixisenatide, a shorter-acting compound known to achieve higher CNS exposure. The persistence of benefit after a two-month washout in that study further suggests that continuous receptor activation within the central nervous system—rather than cumulative peripheral exposure—is critical for neuroprotective efficacy. These findings imply that the pharmacologic design and delivery kinetics of each GLP-1 analogue may substantially influence its neurological outcomes.

The real-world study by Siddeeque et al. (10) complements these clinical trials by providing epidemiologic evidence that long-term GLP-1 RA exposure is associated with a lower incidence of neurodegenerative diseases, including PD, Alzheimer's, and Lewy body dementia. Within this vast cohort exceeding five million participants, semaglutide users demonstrated a significantly reduced risk of PD (RR 0.57; 95 % CI 0.37–0.89), suggesting that structural differences among GLP-1 analogues may translate into divergent neuroprotective effects. Semaglutide's enhanced lipophilicity and prolonged receptor engagement may facilitate superior blood–brain barrier permeability, a pharmacologic distinction that could explain its broader benefits observed in both metabolic and cognitive domains (13). These observational findings lend further weight to the notion that chronic incretin receptor stimulation modulates shared pathophysiologic pathways across neurodegenerative disorders.

Beyond individual study outcomes, the convergence of evidence supports a broader conceptual shift: the pathophysiology of PD may be inseparable from systemic metabolic health. Insulin resistance, chronic inflammation, and mitochondrial stress constitute overlapping mechanisms linking diabetes mellitus and neurodegeneration (5,15). GLP-1 receptor agonists occupy a unique therapeutic position at this intersection by restoring insulin signaling and energy utilization in neural tissue. Several experimental studies have demonstrated that enhancing neuronal glucose metabolism via GLP-1 signaling protects dopaminergic neurons from oxidative injury and improves synaptic resilience (11,13). Moreover, modulation of AMPK and SIRT1 signaling contributes to mitochondrial rejuvenation, aligning with emerging data that mitochondrial decline precedes neuronal death in PD. Thus, GLP-1 RAs may achieve neuroprotection by simultaneously addressing the metabolic and inflammatory substrates that underlie PD pathogenesis.

The clinical implications of these findings are multifaceted. From a therapeutic perspective, GLP-1 receptor agonists represent one of the few pharmacological classes capable of targeting both metabolic comorbidities and neurodegenerative processes. This dual action is particularly relevant because up to one-third of PD patients exhibit insulin resistance or diabetes, which may exacerbate disease progression and cognitive decline (5). The integration of GLP-1 RAs into PD management could therefore yield compounded benefits—ameliorating systemic metabolic dysfunction while attenuating neuroinflammation and neuronal stress. Additionally, their well-established safety profile in endocrinology, characterized mainly by mild gastrointestinal effects, facilitates their repurposing for neurological use. Compared to other disease-modifying strategies such as gene therapy or neurotrophic factor infusion, GLP-1 RAs offer a non-invasive, pharmacologically accessible alternative with global availability and cost-effectiveness.

Nevertheless, translation into routine neurologic practice remains premature. The magnitude of clinical improvement observed across trials remains modest, typically around three to five MDS-UPDRS points, a change that—while statistically significant—may not yet meet patient-perceived thresholds for functional improvement. Furthermore, inconsistencies in dosing frequency, drug formulations, and outcome measurement scales have impeded meta-analytic pooling. Some trials evaluated OFF-medication motor performance, while others used ON-medication states, complicating cross-trial comparability. Additionally, few studies systematically stratified patients by disease stage, baseline insulin resistance, or genetic subtype, all of which could influence therapeutic responsiveness. Given the growing recognition that PD is a heterogeneous syndrome encompassing multiple pathobiological subtypes, future trials should incorporate biomarker-based stratification to identify those most likely to benefit from metabolic interventions.

The neutral outcome of Exenatide-PD3 also prompts reconsideration of whether GLP-1 receptor engagement alone is sufficient to achieve meaningful neuroprotection. Recent advances in incretin pharmacology have introduced dual and triple receptor agonists that target GLP-1, glucose-dependent insulinotropic polypeptide (GIP), and glucagon receptors. These next-generation agents demonstrate superior metabolic and anti-inflammatory efficacy in animal models, with preclinical data suggesting even greater neuroprotective potential (Zhang et al., 2019). Comparative clinical

evaluation of these compounds in PD is warranted, as enhanced receptor synergy could address limitations of single-pathway modulation observed in current GLP-1 trials.

The present synthesis also reveals gaps in mechanistic validation. While several trials incorporated neuroimaging endpoints, such as dopamine transporter binding or FDG-PET, these measures often lacked sufficient sensitivity or uniformity. Cerebrospinal fluid biomarkers of neuroinflammation, α-synuclein aggregation, or mitochondrial function were inconsistently reported. Future studies should integrate multimodal biomarkers—including proteomic and metabolomic signatures—to delineate whether observed motor stabilization reflects genuine neuroprotection or delayed symptomatic deterioration. Longitudinal imaging coupled with biochemical indices could clarify the temporal relationship between metabolic modulation and dopaminergic preservations (Kalia & Lang, 2015; Trist et al., 2019; Hölscher, 2014; Siddeeque et al., 2024; Zhang et al., 2019).

Despite methodological limitations, the consistency of directionality across independent trials, combined with convergent mechanistic and epidemiologic support, reinforces the scientific validity of GLP-1 RAs as disease-modifying candidates. Their capacity to influence both metabolic and neurodegenerative pathways positions them uniquely among current pharmacologic options for PD. In addition, emerging data from Alzheimer's disease trial (Brundin et al., 2010) such as the ELAD study, which demonstrated cognitive stabilization with liraglutide (Brundin et al., 2010) suggests that the neuroprotective potential of GLP-1 RAs may extend across disorders characterized by protein aggregation and mitochondrial failure. This cross-disease efficacy further underscores the therapeutic relevance of targeting metabolic resilience as a shared axis of neurodegeneration.

From a broader translational perspective, GLP-1 receptor agonists represent a paradigm shift in the conceptualization of neurodegenerative therapy, from neurotransmitter replacement toward metabolic network restoration. Their integration into future PD treatment frameworks could herald an era where metabolic precision medicine complements dopaminergic therapy. To achieve this, upcoming trials must emphasize optimal dosing regimens, CNS-targeted formulations, and mechanistically enriched endpoints. Moreover, future research should examine potential synergistic effects with existing neuroprotective interventions such as exercise, dietary modulation, and anti-inflammatory agents, which may enhance GLP-1-mediated benefits through convergent pathways.

CONCLUSIONS

The cumulative evidence from this systematic review suggests that GLP-1 receptor agonists may represent a promising disease-modifying therapeutic class in Parkinson's disease, bridging the gap between metabolic modulation and neuroprotection. Early-phase and mid-phase clinical trials consistently demonstrated improvements or stabilization of motor symptoms, with benefits persisting even after treatment cessation—an observation not characteristic of standard dopaminergic therapy. The underlying mechanisms appear multifactorial, encompassing enhanced mitochondrial function, reduced neuroinflammation, and improved neuronal insulin sensitivity.

However, heterogeneity in trial design, dosing schedules, and CNS bioavailability among different GLP-1 analogues remains a major limitation to confirming definitive efficacy. The negative results of the large phase 3 Exenatide-PD3 trial, juxtaposed with the positive findings of the Lixisenatide and early exenatide studies, underscore the complexity of translating biological plausibility into consistent clinical benefit. Meanwhile, observational evidence continues to strengthen the hypothesis that chronic GLP-1 receptor activation may reduce neurodegenerative risk at a population level.

Future research should focus on next-generation incretin-based agents—such as semaglutide and dual GLP-1/GIP receptor agonists—that demonstrate superior CNS penetration and sustained receptor engagement. Well-powered multicenter trials incorporating biomarker-based endpoints, neuroimaging, and metabolic profiling are required to determine whether GLP-1 receptor activation can truly alter the neurodegenerative trajectory of Parkinson's disease. If validated, this therapeutic

approach could inaugurate a new paradigm of metabolic neuroprotection, redefining disease modification through pathways that restore cellular energy homeostasis rather than merely replenishing dopamine.

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