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# Bridging Metabolism and Neurodegeneration: Antidiabetic Drugs as Therapeutics for Parkinson's Disease

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ABSTRACT: Neurodegenerative and metabolic disorders were historically studied in isolation, but there is growing evidence in recent years that suggests they are more interconnected than originally thought. This review looks at Parkinson's Disease (PD), the world's second most common neurodegenerative disease, and Type 2 Diabetes Mellitus (T2DM), a widespread metabolic disease. Both disorders predominantly affect older populations and share astonishingly similar pathologies and mechanisms. Recent studies have begun to explain their comorbidity not as a coincidence, but as a consequence of the interconnected nature of metabolic and neurodegenerative disorders. This review explores their overlaps to improve the understanding of T2DM and PD and the current cross-treatment approach for both conditions. The shared core dysfunctions of PD and T2DM not only link the two diseases but also offer cross-treatment potential. Ultimately, this overlap is crucial in introducing new therapeutic opportunities and guiding research to more integrated, effective cross-treatment strategies in the future.

KEYWORDS: Translational Medical Sciences, Disease Treatment and Therapies, Parkinson's Disease, Type 2 Diabetes Mellitus, Cross-Disease Treatment.

## Introduction

About 10% of adults have type 2 diabetes mellitus (T2DM), and 1% of people over 60 suffer from Parkinson's disease (PD).[1] With aging populations and longer life expectancies, PD cases are expected to more than double between 2015 and 2040.[2] Neurological and metabolic disorders once viewed as distinct entities are increasingly seen as connected, and studying their intersection can reveal new ways to prevent and treat these conditions. PD is a long-term neurodegenerative illness that becomes more common as people age.1 Its motor symptoms include tremor, bradykinesia, rigidity, postural instability, speech changes, and altered handwriting. Non-motor features include sleep disturbances, depression, cognitive changes, illusions, and delusions.[3,4] At the tissue and molecular level, PD is steadily progressive and involves degeneration of nigrostriatal dopaminergic neurons and alterations in central and peripheral tissues. It is driven by mechanisms such as protein aggregation, lysosomal and mitochondrial dysfunction, and chronic inflammation.[5] Diabetes mellitus is the most common long-term metabolic disease globally and poses a significant public health challenge due to its prevalence, disability, and mortality.[6] T2DM is a chronic condition defined by insufficient insulin secretion from pancreatic beta cells relative to the body's insulin resistance, leading to issues with glucose metabolism and chronic inflammation. The progression of T2DM is linked to various complications such as vision loss, stroke, kidney failure, heart attacks, limb amputation, and neuropathy.[7]

This review explores the important mechanistic pathways PD and T2DM share, and how these shared pathways can guide the repurposing of treatments. After reviewing the epidemiological and clinical overlaps to explain comorbidity, shared pathophysiology is synthesized to highlight important mechanisms. Next, pharmacological evidence is evaluated. Finally, findings are integrated to discuss limitations and prioritize research directions. This paper's central hypothesis is that understanding how metabolic and neurodegenerative diseases are related can improve cross-treatment medications that take a mechanistic approach towards PD. Research suggests some diabetes medications may offer neuroprotection benefits, though cautious interpretation is necessary due to translational limitations and gaps in mechanistic understanding.

## PD and T2DM Comorbidity

Epidemiologic studies have long suggested a connection between T2DM and Parkinson's disease, and this section summarizes some of the biological evidence that supports this comorbidity. Sandyk and colleagues first described an association in 1993, where they noted that PD patients who also had T2DM experienced worse motor symptoms and reduced response to treatment.[8] Another early work reported a high prevalence of impaired glucose tolerance among PD patients (50-80%), though more recent findings suggest that overt impairment actually only occurs in roughly one-fifth of patients.[9] Large prospective data support this relationship as well. In the NIH-AARP cohort, Xu *et al.* found that T2DM predicted a higher future risk of PD, particularly for people with longer diabetes duration. This effect persisted across demographic subgroups and after excluding major comorbidities.[10] A modern meta-analysis of observational studies by Chohan *et al.* also corroborated that T2DM raises the future risk of PD. It provided evidence that diabetes may accelerate motor progression with more modest evidence for cognitive decline.[11] In one of the largest observational cohorts, Athauda *et al.* analyzed Parkinson's data and found that PD patients with comorbid T2DM had worse motor and nonmotor symptom scores at



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baseline, were more likely to report loss of independence and depression, and showed faster motor decline. They also had worse mood, more gait impairment, and a higher risk of mild cognitive impairment compared with PD patients without T2DM.[12]

However, epidemiologic findings require cautious interpretation since the bulk of data comes from people of European ancestry and may not generalize globally. An important limitation is that groups at highest risk for T2DM, such as South-Asian and African-Caribbean populations, were underrepresented, making it difficult to conclusively interpret results.[13] Diabetes prevalence and its cognitive consequences may vary across ethnic groups. For example, one cohort reported diabetes prevalence of 30% in Hispanics and a T2DM-associated mild cognitive impairment risk of 11% in Hispanics versus 4.6% in non-Hispanics.[14] Differences in diabetes prevalence across populations may partly explain variation in PD frequency and clinical phenotype.[15]

Despite their complexity, both PD and T2DM are common disorders with emerging hope for shared therapeutic strategies. Their comorbidity provides a strong rationale for prioritizing antidiabetic agents for evaluation, and the mechanistic basis of this relationship is examined in the next section.

## Shared Pathophysiology

This section synthesizes mechanistic evidence linking PD and T2DM and highlights how these mechanisms can create cross-disease therapeutic opportunities.

### *Insulin Dysregulation:*

Insulin, secreted by pancreatic β cells, is a key metabolic hormone that mediates its effects via the insulin receptor.[16] It regulates cellular energy use, glucose uptake, growth, repair, gene expression, mitochondrial activity, autophagy, and protein synthesis. Insulin receptor signaling activates PI3K and Akt/PKB, key intracellular signaling kinases, as well as PPARs and mTOR, regulators of metabolism and growth. It also activates transcription factors like NRF1/2 that coordinate mitochondrial function and antioxidant responses, thereby supporting metabolism, mitogenesis, synaptic function, and defenses against oxidative stress.[17, 18] This peptide hormone also regulates peripheral glucose transport and has been shown to cross the blood-brain barrier (BBB) via insulin transporters.[19] Once in the brain, insulin acts directly on receptors on neurons, astrocytes, and microglia.[20, 21] Insulin resistance, defined as reduced tissue responsiveness to insulin, is a hallmark of T2DM and has been linked to the development of neurodegenerative disorders.[22, 23]

Considerable evidence ties abnormalities in insulin signaling, both peripheral and central, to Alzheimer's disease and cognitive decline, and interest is growing in similar processes in PD.[24] Preclinical work shows that diet-induced insulin resistance impairs nigrostriatal dopamine function, a core feature of PD neuropathology.[25] Insulin-resistant models, including the db/db mouse, demonstrate related neurodegenerative changes, and insulin resistance has also been experimentally associated with increased α-synuclein accumulation in the midbrain and substantia nigra.[26, 27] Clinically, greater insulin resistance in PD patients has also been linked to increased severity of non-motor symptoms.[28]

Efforts to probe causality used models such as the MitoPark mouse and complementary *in vitro* and *ex vivo* approaches, showing that insulin resistance worsens pathological PD features.[29] In those settings, insulin resistance promoted α-synuclein aggregation in dopaminergic neurons, increased reactive oxygen species, and induced mitochondrial dysfunction, impairing cellular energy production. Clinically, a study of 154 non-diabetic PD patients found a high prevalence of insulin resistance based on abnormal HOMA-IR scores (58%), a calculation to estimate resistance levels.[30] Analyses of blood-neuron-derived extracellular vesicles, lipid nanoparticles that cross the BBB and enter the bloodstream, have also shown altered IRS1 phosphorylation correlating with tremor severity in PD patients. IRS1 is an important protein for cell signaling for insulin.[31] However, findings are not completely uniform. Peripheral insulin sensitivity measured by hyperinsulinemic-euglycemic clamp, a research method where insulin is infused while blood glucose is held constant, showed little difference between some PD patients and controls. As such, the role of peripheral insulin abnormalities in PD remains debated.[32]

Meanwhile, direct assessment of brain insulin signaling identified abnormalities in the dorsolateral prefrontal and posterior parietal cortex only in cognitively impaired patients, not in cognitively normal individuals.[33] Supporting this, analyses of patient brain tissue indicate that components of insulin/IGF-1 signaling, including IRS1/2 and downstream kinases such as Akt and mTOR, can be inactivated in neurodegenerative diseases, mirroring peripheral insulin resistance.[34] Importantly, brain insulin desensitization in neurodegenerative disease is not solely explained by hyperglycemia or hyperinsulinemia because similar desensitization is observed in AD patients without diabetes.[35] Rather, chronic neuroinflammation likely drives insulin desensitization as pro-inflammatory cytokines such as TNF can block growth factor signaling. These include insulin and IGF-1 pathways.[36] Given insulin's role in neuronal growth and repair, desensitization can render neurons vulnerable to cumulative damage. Cortical neurogenesis is negligible in such cases, and neuronal loss accumulates over time.[37] Consistent with this, multiple preclinical PD models exhibit impaired insulin signaling with downstream effects that plausibly contribute to disease pathology.[38] While causation is not settled, evidence suggests impaired insulin signaling is detrimental and may contribute to PD-related neurodegeneration.

### *Amyloid Aggregation:*

Both T2DM and PD involve the accumulation of misfolded amyloid proteins. Most diabetes patients display islet amyloid polypeptide (IAPP) deposits in pancreatic β cells, which impair cellular function and promote cell death.[39] Recent work has examined interactions between α-synuclein and IAPP.[40] *In vitro* experiments suggest that α-synuclein and IAPP can cross-seed each other's aggregation and amyloid formation.[41]

***Microglial Activation and Chronic Inflammation:***

Microglia, the brain's resident phagocytic immune cells, normally clear damaged neurons and release neuroprotective factors to support synaptic regeneration.[42] They can be activated by stimuli such as lipopolysaccharides to a pro-inflammatory state, expressing cytokines like TNFα, IL-1β, and IL-6 and triggering neuroinflammation.[43] Imaging studies in small PD cohorts have demonstrated increased microglial activation on PET scans.[44] Consistent with this, patients with PD often show elevated concentrations of IL-1β, IL-6, and TNFα in the brain.[45] While initial microglial activation may be neuroprotective, prolonged activation tends to have harmful effects and can accelerate PD progression.[46, 47] Insulin resistance influences microglial activation and neuroinflammation through NF-κB and PI3K/Akt signaling. These are pathways that regulate microglial phenotype and inflammatory mediator expression.[43] Pro-inflammatory cytokines like TNFα can induce IRS1 inactivation, thereby blocking downstream signaling in a vicious cycle and resulting in the accumulation of advanced glycation end-products (AGEs).[5, 48] AGEs have been detected in vulnerable brain regions such as the substantia nigra, and AGE-RAGE interactions activate pathways that cause oxidative stress, inflammation, and neuronal death.[49] Intriguingly, AGEs have also been found colocalized with α-synuclein in abnormal deposits of protein called Lewy bodies.[50] Glycation of α-synuclein, a covalent reaction involving the attachment of sugar-derived metabolites, promotes toxic oligomer formation via cross-linking and appears to worsen PD progression.[49] Glycation agents like methylglyoxal also impair α-synuclein clearance by inhibiting ubiquitin-proteasome and lysosomal degradation pathways, promoting accumulation and potentially exacerbating PD.[5]

***Oxidative Stress and Mitochondrial Dysfunction:***

Mitochondrial dysfunction is an early central event in PD pathogenesis, and many neurotoxins used to model Parkinsonism exert their effects by targeting mitochondria.[51, 52] Elevated oxidative stress is also a defining feature, caused by dysfunctional insulin signaling.[53] Chronic insulin resistance in diabetic models such as db/db mice has caused mitochondrial disruption and dopaminergic neuronal degeneration. The IRS1 and IRS2 insulin signaling branches, key mediators of insulin's effects on metabolism, regulate processes like glucose and lipid homeostasis. Rodent studies also show that they regulate FOXO1 via the PI3K/Akt pathway. FOXO1 is a transcription factor involved in metabolism and oxidative stress response, and disruption of these pathways can lead to impaired ATP generation and increased reactive oxygen species.[54-56] This links mitochondrial dysfunction and oxidative stress to processes important in diabetes and PD pathogenesis.

**Table 1:** Summary of where PD and T2DM mechanisms converge and how they interact.

| Shared Mechanism | Converging Evidence | Mechanisms Impacted / Interaction | Biomarkers |
|---|---|---|---|
| **Insulin Dysregulation** | Central and peripheral insulin resistance in PD | Amyloid: reduced autophagy → increased α-synuclein<br>Mitochondria: PI3K/Akt disruption → reduced ATP, increased ROS<br>Microglia: NF-κB signaling → increased pro-inflammatory cytokines | IRS1-P, HOMA-IR |
| **Amyloid Aggregation** | Cross-seeding between pancreas and brain (IAPP and α-syn) | Clearance: glycation → reduced UPS/lysosome degradation<br>Inflammation: AGE-RAGE → TNFα/IL-6 elevation<br>Mitochondria: oligomer stress → increased ROS | α-synuclein oligomers, IAPP |
| **Neuroinflammation** | Elevated cytokines and activated microglia in PD | Insulin: TNFα → IRS1 inactivation, insulin desensitization<br>Clearance: impaired phagocytosis → α-syn accumulation<br>Neurons: cytokine signaling → oxidative damage | IL-1β, TNFα, AGEs |
| **Mitochondria Dysfunction / Oxidative Stress** | Early PD pathology, worsened by insulin resistance | Proteostasis: ROS → protein misfolding, α-syn accumulation<br>Insulin: mitochondrial failure → impaired PI3K/Akt<br>Energy: ATP loss → synaptic dysfunction | ROS levels, mtDNA damage |

## ■ Pharmacological Overlap and Repurposed Interventions

This section evaluates antidiabetic agents in the context of the shared mechanisms summarized in Table 1. Current clinical care for Parkinson's disease focuses on replacing dopamine to relieve symptoms, but such therapy has not convincingly altered disease progression.[57] Despite growing prevalence and rising economic burden, new drugs for PD to date have produced only marginal improvements in outcomes.[58] Parkinson's pathology is complex and involves α-synuclein accumulation together with inflammation, synaptic dysfunction, and loss of dopaminergic neurons. Evidence also points to insulin resistance as an additional component. Because single drugs usually target individual pathological pathways, an effective disease-modifying strategy might require either combinations of agents that address multiple mechanisms or a single compound able to act on several of these processes.[59] In this section, commonly used antidiabetic agents that have potential as cross-treatments for PD and T2DM will be looked at.

***Metformin Hydrochloride:***

Metformin is a principal first-line drug for T2DM with antihyperglycemic effects. It has a wide range of pleiotropic actions, like activation of AMPK, a cellular energy sensor, and reduction of hepatic glucose output. It also decreases advanced glycation end products and reduces endothelial reactive oxygen species. Additionally, it regulates glucose and lipid metabolism in cardiomyocytes, which may lower cardiovascular risk. Metformin has reported to have anticancer, antiproliferative, and apoptosis-inducing effects that could affect malignancies in several organs, and preclinical work has also suggested neuroprotective effects across disorders, including PD, AD, multiple sclerosis, and Huntington's disease.[60] α-synuclein accumulation is a recognized feature of neurotoxicity in PD, and in preclinical models, metformin reduced the number of α-synuclein-positive cells.[61, 62] It also protected dopaminergic neurons from degeneration by reducing lipid peroxidation in rotenone-treated mice while enhancing phosphatase activity in an MPTP mouse model. This led to reduced α-synuclein


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phosphorylation in the substantia nigra.[63, 64] Together, these findings support metformin's potential as a disease-modifying agent in PD, though evidence remains preclinical. Clinical and observational data are currently inconsistent. In the Tracking Parkinson's cohort, Athauda *et al.* found no protective effect in diabetic PD patients, with worse cognitive scores at 36 months in metformin users.[12] Clinical trials are also scarce, often combining metformin with other oral agents, and current evidence does not support a therapeutic effect in humans.[65]

***Insulin:***

As covered before, insulin plays a central role in both PD and T2DM pathology. Consequently, trials are underway testing intranasal insulin for neurodegenerative disorders, enabling direct central nervous system (CNS) delivery.[66] In a pilot study of 104 patients with amnestic mild cognitive impairment (MCI) or early AD, intranasal insulin at 20 or 40 International Units (IU) improved ADAS-Cog 12 scores, a 12-item scale evaluating cognitive function, compared with placebos. Additionally, delayed recall benefits persisted two months after stopping treatment in the 20 IU group. Intranasal insulin also prevented declines in cerebral glucose metabolism in that work.[67] Because early results were encouraging, Craft and colleagues performed a 12-month phase 2/3 study of 40 IU intranasal insulin daily in 289 patients with MCI or AD.[68] That larger trial failed to show improvements in primary or secondary outcomes at 12 months or after a subsequent open-label period, which suggests that intranasal insulin did not provide symptomatic or disease-modifying benefit in that sample. Device differences in delivery may have contributed because patients treated with the original device showed near six-point ADAS-Cog improvements and changes in CSF biomarkers at 18 months.[66] Genetic factors can also influence response. A separate small trial of 60 MCI or probable AD patients reported that 40 IU intranasal insulin detemir improved cognition with effects that depended on ApoE genotype, with memory improvement in ApoE ε4 carriers and worsening in noncarriers.[69] This shows that genetic factors can influence response, but consistent biomarkers or functional measures would be more reliable signs of efficacy. More recently, intranasal insulin was evaluated in PD. In a 4-week pilot trial, verbal fluency rose in the intranasal insulin arm while it fell in the placebo group. Motor performance and function also improved from baseline in the insulin group, yielding a lower disability score. These preliminary findings suggest feasibility but require confirmation in larger trials.[70]

***SGLT2 Inhibitors:***

Sodium glucose cotransporter 2 inhibitors, originally developed to lower blood glucose in T2DM, have also demonstrated cardioprotective benefits in clinical trials.[71, 72] Preclinical studies suggest SGLT2 inhibitors can reduce neuroinflammation, support neuronal plasticity, and restore mitochondrial function. These are all mechanisms that could alter dementia and neurodegeneration risk. Additionally, prior observational studies have explored associations with cognitive outcomes. However, results are mixed, mostly observational, and do not yet establish causality.[73-75] A pooled meta-analysis of 12 randomized controlled trials covering 74,442 patients found no significant association between SGLT2 inhibitor use and risk of dementia, its subtypes, or Parkinson's disease when compared with controls.[76] At the moment, further long-term randomized clinical trials are necessary to clarify whether SGLT2 inhibitors have therapeutic relevance in neurodegenerative diseases.

***GLP-1 Receptor Agonist:***

GLP-1 is a gut-derived incretin hormone released after eating, and it binds to its receptors to trigger intracellular signaling central to cell growth and repair. It regulates metabolic homeostasis by stimulating glucose-dependent insulin secretion from beta cells, inhibiting glucagon release from alpha cells, slowing gastric emptying, and reducing food intake.[77] GLP-1 receptor agonists mimic these effects both peripherally and centrally, and while native GLP-1 is rapidly degraded by an enzyme known as DPP-4, GLP-1 receptor agonist analogs resist degradation. Compared to a half-life of one to two minutes, extended stability gives these medications more time to exert their effects.[78] These agonists have been used safely and effectively in T2DM as they do not induce insulin desensitization or hypoglycemia in normoglycemic subjects.[79] GLP-1 is produced in brain regions including the nucleus of the solitary tract, intermediate reticular nucleus, piriform cortex, and olfactory bulb. Receptors are present in nuclei of the brainstem, the hypothalamus, and in limbic areas. Central GLP-1 receptor effects have been examined mainly in animal models. Receptor distribution has been reported in the frontal and occipital lobes, hypothalamus, thalamus, hippocampus, cerebellum, and substantia nigra.[80-84]

GLP-1 and its analogs can cross the BBB in some contexts, and neuronal synthesis in the nucleus of the solitary tract has motivated preclinical studies of these incretin agonists in neurodegeneration.[85] However, BBB penetration varies by compound. Rodent pharmacokinetic studies show that liraglutide and semaglutide do not measurably cross the BBB, suggesting indirect or peripheral mechanisms. Meanwhile, exenatide and lixisenatide do cross the BBB and may therefore offer advantages for AD and PD.[86] Preclinical data further indicate that GLP-1 receptor activation protects against cytokine-mediated apoptosis and may stimulate neurogenesis.[87] Mechanistically, GLP-1 acts through a G-protein-coupled receptor to activate cAMP/PKA and PI3K signaling via Akt, PKC, and MAPK. These are intracellular pathways involved in metabolic regulation, cell survival, and plasticity. Its relevance to PD involves MAPK/ERK1/2 pathways important for synaptic plasticity, together with PI3K-Akt signaling that elevates cAMP and PKA to support neuronal survival.[88] The Akt pathway phosphorylates multiple downstream substrates that regulate synapse formation, autophagy, and long-term potentiation, important processes for neuronal maintenance. Concurrently, Akt signaling suppresses pro-inflammatory cytokine release, apoptosis, microglial activation, tau phosphorylation, and the accumulation of α-synuclein and Aβ, making GLP-1 signaling a compelling PD target.[89, 90] Recent evidence also suggests GLP-1 may help maintain BBB integrity, rep-

resenting an additional neuroprotective mechanism requiring further investigation.[91]

In PD models, exendin-4 reduces microglial activation and dopaminergic neuron loss in the substantia nigra and striatum.[92] Li and colleagues found neuroprotection with exenatide in cultured cortical and ventral mesencephalic dopaminergic neurons and improved motor activity in MPTP mice, a toxin-induced model.[93] While promising, translation to humans is ongoing. Observational and cohort studies indicate lower PD prevalence among diabetic patients on GLP-1 receptor agonists or DPP-4 inhibitors. One large study reported PD risk was 36% lower for DPP-4 users and 62% lower for GLP-1 agonist users relative to other oral antidiabetic drugs.[94,95] These findings could imply the protective effect of incretin-based therapies, but clinical trials are mixed. A small randomized single-center trial of once-weekly exenatide improved motor function off medication but not while participants were on their usual PD drugs.[96] A phase 2 trial of NLY01, a pegylated exenatide analog, showed no benefit in early untreated PD.[97] Additionally, a double-blind phase 2 trial of lixisenatide slowed motor disability progression at 12 months but caused gastrointestinal side effects.[98] Together, these findings highlight both the therapeutic potential and current limitations of GLP-1 receptor agonists for neurodegeneration.

## GLP-1 / GIP Dual Agonists

GIP is the sister incretin hormone to GLP-1, and the two share closely related physiological roles.[99] It is a 42-amino-acid peptide expressed in multiple cell types, including neurons. Its receptor is a seven-transmembrane G-protein-coupled receptor of the glucagon family that, similar to GLP-1, elevates cAMP, a second messenger molecule.[100, 101] GIP receptor expression has been documented in large neurons such as cortical pyramidal cells, hippocampal pyramidal neurons, dentate gyrus granule cells, cerebellar Purkinje cells, and basal brain regions. GIP is expressed in the adult hippocampus and can induce progenitor proliferation.[102, 103] In a comparative pesticide cell model using GLP-1 analogs, GIP analogs, oxyntomodulin, and DA1-JC, a dual agonist, DA1-JC was most effective at protecting SH-SY5Y cells from rotenone stress.[104] That finding supports the idea that GIP can augment the neuroprotective actions of GLP-1 receptor stimulation. In MPTP mice, DA1-JC produced limited protection but reduced motor impairment, normalized synapse numbers, protected substantia nigra neurons, decreased chronic inflammation, and increased BDNF.[105] Because GIP and GLP-1 engage complementary protective signaling, combined GLP-1/GIP agonists are under development for T2DM, with animal studies demonstrating additive benefit over single agonists.[106]

Several dual agonists have reached clinical trials for T2DM and outperformed liraglutide on metabolic endpoints.[107] For example, DA-CH3 protected dopaminergic neurons, reduced inflammation, and improved MPTP-induced motor deficits more than liraglutide.[108] In other MPTP models, DA4-JC and DA-CH5 provided the strongest neuroprotection by improving motor function, preserving dopaminergic neurons, reducing inflammation, and restoring glial-derived neurotrophic factor (GDNF), a crucial protein for neuronal survival.[109] DA-CH5 also outperformed exendin-4, reduced α-synuclein, restored brain-derived neurotrophic factor (BDNF), and lowered pro-inflammatory cytokines in MPTP mice. Meanwhile, DA4-JC rescued motor deficits in rotenone models via mitochondrial restoration through Akt-JNK signaling.[108, 110, 111] Dual agonists such as DA4-JC are notable for enhanced BBB penetration and potentially more balanced weight-loss effects than single agonists, improving tolerability.[85, 112] Collectively, these findings position GLP-1/GIP dual agonists as promising candidates for neurodegenerative diseases.[113]

## Discussion

**Table 2:** Summary of current PD-T2DM therapies, their benefits, and potential areas for future research.

| Agent | Effects | Mechanism | Evidence level | Current gaps |
|---|---|---|---|---|
| **Metformin** | Lowers ROS and α-synuclein, increases autophagy | AMPK activation and decreased AGE formation | Preclinical benefit, clinical inconsistency | Lack of RCTs; mixed observational results |
| **Intranasal Insulin** | Restores brain insulin signaling | Activates CNS insulin receptors | Success in pilot trials, unclear benefit in larger trials | RCT negative, device and genotype effects |
| **SGLT2 Inhibitors** | Lowers neuroinflammation, mitochondrial support | Inhibition of renal SGLT2 receptors, reduces inflammation and oxidative stress | Observational and preclinical with mixed clinical results | No demonstrated benefit in RCTs, lacking long-term evidence |
| **GLP-1 RAs** | Reduces inflammation, improves neuronal and pancreatic beta cell survival | GLP-1R activation, activation of cAMP/PKA, PI3K/AKT, and MAPK/ERK pathways | Preclinical and observational human data but mixed clinical trials; promising | Heterogeneity between compounds, mixed clinical results |
| **GLP-1 / GIP dual agonists** | Enhances neuroprotection, broader effects across different mechanisms | Dual GIP-1/GIP receptor activation | Robust and promising but limited human data | Large PD trials lacking |

PD is currently the second most common neurodegenerative disease globally, affecting more than ten million individuals. There have been many advances in our understanding of the pathogenesis and epidemiology of PD, but there are many gaps in current research. Table 2 summarizes the main drugs this paper covers, as well as their current limitations. One major gap in research in this field that needs to be covered is the translation from animal models to humans. Many drugs show early promising effects in cells and animal models, but show weak or mixed signals in humans. One example of this is metformin, which works well in MPTP and rotenone models, but did not show any benefit in the Tracking Parkinson's Cohort. SGLT2 inhibitors also show potential in lab and animal studies, but did not demonstrate benefit for PD in a pooled human trial, showing that species differences between animal models and humans are a major translational gap. Biomarkers have also been historically limited in their use, specifically in the early stages of PD. There have been recent advances, but their significance for future research remains. Biomarkers paired with the mechanisms summarized in Table 1 can help confirm medication functionality, like CSF α-synuclein seeding assays for aggregation, IRS1 phosphorylation in neuron-derived extracellular vesicles for insulin signaling, and plasma or CSF AGE markers for glycation stress. Ensuring target engagement is key for translation. Another gap is the lack of randomized


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controlled trials (RCTs) for promising medications, which brings the risk of confounding by differences in healthcare access or polypharmacy. Randomized proof-of-principle studies can help establish causality.

Negative results can also arise from a lack of follow-up, differences in brain exposure, and dose response. LIXIPARK, one of the stronger trials to date, only had 12 months of follow-up so far, which could be an insufficient timeline to capture the progressive nature of PD. Phase studies that test multiple doses and monitor CSF and blood biomarkers over the course of longer timeframes, like 24-36 months, can help identify trends. Other complicating factors include differences in host biology and delivery methods. Intranasal insulin showed benefits in a pilot trial, but such improvements did not translate to a larger 12-month Alzheimer's trial. This could have been impacted by factors like the APOE genotype as well as differences in devices. Thus, it would be beneficial for future trials to record delivery parameters and also consider genotype variations.

It is also crucial to consider variations among compounds within the same drug class. Exenatide and lixisenatide were able to cross the BBB in a rodent study, but liraglutide and semaglutide did not. Since the BBB acts as a filter into the brain, this is a significant difference between incretin therapies, and peripheral metabolic effects do not guarantee neuroprotection. This relates to exposure gaps as well, where CNS engagement is not verified. CSF drug levels, TSPO PET scans for inflammation, and DAT imaging for dopaminergic neuron monitoring can all be used to verify whether a drug truly affects the CNS. Another significant gap is heterogeneous preclinical models, as different animal models can yield different outcomes. This carries the risk of advancing drugs that only work in narrow settings, and can be addressed by using complementary animal models and analyzing shared biomarker patterns. Safety and tolerability are also important to note in future research, as lixisenatide gastrointestinal (GI) side effects can limit long-term benefit. Standardized safety reporting can address tolerability, and outcome measures like wearable gait metrics can connect pathophysiology to clinical outcomes.

Study design is also important to consider. Many retrospective trials relied upon patients' recollection of their symptoms, creating potential inclusion and recall bias. Additionally, heterogeneous clinical research varies widely in design, disease stage, and outcomes measured. Claims of lower PD incidence with some diabetic drugs could also be affected by factors like differences in healthcare access and polypharmacy. Patients with longstanding T2DM also frequently develop multiple organ system failure, such as heart failure, coronary disease, chronic kidney disease, and peripheral vascular disease. This presents a unique challenge when conducting large clinical trials, as high morbidity and mortality might impact the outcome of these trials, creating survival bias. This is particularly true if one is to conduct multiple years longitudinal study. Additionally, as mentioned earlier, population differences are a major hurdle in current PD and T2DM research. Some groups show greater insulin resistance compared to others who express more beta-cell dysfunction. Genetic differences can also shape how factors like high blood sugar and protein modification influence disease progression, so research should move from conventional broad associations. Relying less on self-reported race and focusing on genetic ancestry markers while studying more diverse populations is important to ensure repurposed therapies are not limited to historically studied populations. Population stratification analyses and specifying metabolic phenotypes are essential for reducing bias in future research. Dual agonists with promising preclinical results and brain penetration, like DA-CH5 and DA-4JC, are good candidates for more extensive mechanistic investigations.

## ■ Conclusion

This review supports the central thesis that PD and T2DM are biologically linked and that antidiabetic medications are promising candidates for repurposing in PD. Experimental and epidemiological evidence confirms this, demonstrating that metabolic pathways influence neurodegenerative processes.

Some potential candidates are entering late-stage clinical evaluation. They target pathways such as GLP-1, GIP, and insulin signalling and may produce neuroprotective effects against features of PD progression by enhancing autophagy, increasing neuronal survival, reducing apoptosis and oxidative stress, as well as alleviating neuroinflammation and insulin resistance. The pathological hallmarks of PD, like dopaminergic neuronal loss and α-synuclein aggregation, may be targeted via signalling cascades, such as engagement of PI3K/Akt and GSK3β. GLP-1 receptor agonists have been demonstrated to reduce inflammation and oxidative stress, prevent the accumulation of the characteristic toxic proteins, and influence impaired insulin signalling. GLP-1/GIP dual agonists also have great potential and warrant evaluation in human trials, especially as these dual receptor agonists have a more balanced influence on weight loss than single receptor agonists. Other agents available for the treatment of diabetes, including metformin and SGLT-2 inhibitors, have shown promise in the initial stages of evaluation for PD.

At present, many results are still unclear, controversial, and need more research. Several key questions remain unanswered about the efficacy of different cross-treatment agents, how much of a central impact they have, and how they should be timed and distributed. Nevertheless, the approach to drug repurposing outlined in this paper has wide implications for cross-therapeutic treatments. By targeting underlying pathological similarities, treatment can shift from isolated diagnoses to coordinated strategies targeting intersecting mechanisms. Biological insights can guide clinical testing and application. Ultimately, the bridge between PD and T2DM and metabolic and neurodegenerative disorders is a powerful one that science must continue to explore.

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