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REVIEW ARTICLE

Repurposing Antidiabetic Agents as Potential Therapeutics in Neurodegenerative Diseases: Current Status and Future Perspectives

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Repurposing Antidiabetic Agents as Potential Therapeutics in Neurodegenerative Diseases: Current Status and Future Perspectives

SUMMARY

This review focuses on preclinical, clinical, and epidemiological studies that highlight the therapeutic potential of antidiabetic drugs for the prevention and treatment of neurodegenerative diseases. Neurodegenerative disorders represent a significant public health concern, with their global prevalence steadily increasing. These conditions are progressive and heterogeneous, substantially reducing quality of life and imposing a considerable burden on healthcare systems and society. The rising disability, morbidity, and mortality associated with these diseases coincide with the aging of the global population. Due to their complex etiology and progressive nature, neurodegenerative diseases pose considerable challenges for diagnosis and treatment. Current therapies are primarily limited to alleviating cognitive and/or motor symptoms and are generally insufficient to slow, halt, or prevent disease progression. Consequently, there is an urgent need for novel interventions that can enhance neuronal function and attenuate underlying disease mechanisms. Recent evidence from preclinical and clinical studies has revealed significant links between diabetes and neurodegenerative diseases. This review aims to guide future research by providing an up-to-date overview of the effects of antidiabetic agents on neurodegenerative disorders.

Keywords: *Neurodegenerative diseases, type 1 diabetes mellitus, type 2 diabetes mellitus, insulin resistance, antidiabetic drugs.*

Antidiyabetik İlaçların Nörodejeneratif Hastalıklarda Yeniden Konumlandırılması: Güncel Durum ve Gelecek Perspektifleri

ÖZ

Bu derleme, antidiyabetik ilaçların nörodejeneratif hastalıkların önlenmesi ve tedavisindeki terapötik potansiyelini ortaya koyan preklinik, klinik ve epidemiyolojik çalışmalara odaklanmaktadır. Nörodejeneratif hastalıklar dünyada her geçen gün artan prevalansa sahip, yaşam kalitesini önemli derecede bozan, ilerleyici ve heterojen yapılarıyla sağlık sistemleri ve sosyoekonomik yapı üzerinde ciddi yük oluşturan önemli halk sağlığı sorunlarıdır. Nörodejeneratif hastalıkların yol açtığı sakatlık, morbidite ve mortalite oranlarındaki artış dünya nüfusundaki yaşlanma hızına paralel artmaktadır. Nörodejeneratif hastalıklar karmaşık etyolojileri ve ilerleyici yapıları nedeniyle tanı ve tedavide önemli zorluklar ortaya çıkarmaktadır. Son yıllarda bu hastalıkların altında yatan temel mekanizmaları anlamak için büyük ilerlemeler kaydedilmiş olsa da mevcut tedaviler sadece bilişsel gerilemeyi ve/veya motor semptomları hafifletebilmekte, hastalığı yavaşlatma, durdurma veya önleme konusunda yetersiz kalmaktadır. Bu bağlamda nöronal işlevi iyileştirecek ve altta yatan hastalık süreçlerini yavaşlatacak güncel tedavilere acil ihtiyaç vardır. Son yıllarda gerçekleştirilen çalışmalardan elde edilen kanıtlar diyabet ve nörodejeneratif hastalıklar arasında önemli bağlantılar olduğunu ortaya koymuştur. Bu derlemenin temel amacı, bu alandaki araştırmacılara, antidiyabetik ajanların nörodejeneratif hastalıklardaki etkilerini değerlendirmeleri için güncel bir bakış açısı sunarak, gelecekteki bilimsel çalışmalara yön vermektir.

Anahtar Kelimeler: *Nörodejeneratif hastalıklar, tip 1 diabetes mellitus, tip 2 diabetes mellitus, insülin direnci, antidiyabetik ilaçlar.*

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INTRODUCTION

Neurodegenerative diseases (NDs) comprise a heterogeneous group of progressive disorders that involve the accumulation of misfolded intracellular or extracellular proteins, which leads to synaptic dysfunction and ultimately neuronal death (Forrest & Kovacs, 2025). The most prevalent NDs, most prominently Alzheimer's disease (AD) and Parkinson's disease (PD), alongside other conditions like Huntington's disease (HD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS), collectively affect millions worldwide and impose a heavy burden on the functional independence of affected individuals. The prevalence of AD and PD, which are strongly age-associated, has risen sharply in parallel with the global increase in life expectancy (Lamptey et al., 2022). According to the World Health Organization (WHO) (2023), neurological disorders are currently the second leading cause of death globally, responsible for approximately 9 million deaths each year. Despite major advances, the precise pathophysiological mechanisms underlying most NDs remain incompletely understood. Shared molecular pathways include glutamate excitotoxicity, calcium dysregulation, proteotoxic stress, neuroinflammation, mitochondrial dysfunction, and oxidative stress (Jurcau, 2021). These complex etiologies, combined with their progressive nature, pose significant challenges for both diagnosis and therapy, and currently available treatments are limited to symptomatic relief. Hence, there is an urgent need for innovative interventions capable of restoring neuronal function and modifying the underlying disease course.

Developing novel pharmacological compounds is time-consuming, expensive, and often unsuccessful in clinical translation. Therefore, researchers have increasingly turned to drug repurposing, defined as the re-evaluation of approved medications for new therapeutic indications, as a promising and cost-effective strategy. Emerging evidence suggests a strong bidirectional relationship between diabetes mellitus (DM) and NDs, which has garnered growing scientific attention (Szablewski, 2025; Verdile et al., 2019).

DM is a chronic, progressive, and heterogeneous metabolic disorder affecting millions worldwide. As reported by the American Diabetes Association Professional Practice Committee (2024), DM is a metabolic condition marked by sustained elevations in blood glucose levels and impaired glucose regulation arising from defective insulin secretion, reduced tissue responsiveness to insulin, or both processes. Type 1 diabetes mellitus (T1DM) predominantly develops as a consequence of immune-mediated destruction of pancreatic β-cells, ultimately resulting in an absolute lack of endogenous insulin. By comparison, type 2 diabetes mellitus (T2DM), which constitutes nearly 90% of diagnosed cases, is associated with peripheral insulin resistance together with a progressive and relative decline in insulin secretory function (DeFronzo, 2015). Neurological complications such as peripheral neuropathy, retinal neurodegeneration, and diabetic encephalopathy underscore that diabetes extends beyond a metabolic disorder to affect the central nervous system. Indeed, pathophysiological parallels between T2DM and AD have led some researchers to describe AD as type 3 diabetes, highlighting the shared mechanisms of insulin resistance, cognitive decline, and neurodegeneration (Kandimalla et al., 2017).

Epidemiological and experimental studies have revealed that DM significantly influences the incidence and progression of NDs through shared mechanisms, including insulin resistance, impaired glucose metabolism, oxidative stress, mitochondrial dysfunction, and chronic inflammation (Akter et al., 2011; Butterfield et al., 2014; De La Monte, 2017; Li & Hölscher, 2007; Luchsinger et al., 2004). Our prior investigations and research provide a multi-faceted rationale for exploring shared pathways in neurodegeneration. Specifically, our review on Sestrin-2 highlights it as a critical therapeutic target for neuroprotection (Baran,

2022b), while our experimental research into pro-inflammatory cytokines (TNF-α and IL-6) emphasizes the importance of modulating systemic inflammation to mitigate acute toxicity and neuronal damage (Baran et al., 2024). Furthermore, our study on pharmacogenetic variability (Baran, 2022a) underscores that individual differences in drug response must be considered when repurposing antidiabetic agents for neurological indications. These findings collectively support the strategy of targeting metabolic and inflammatory axes to develop more personalized and effective neuroprotective therapies.

Given the biological and epidemiological connections between DM and NDs, the therapeutic repurposing of antidiabetic agents has emerged as a significant area of investigation. Currently approved pharmacotherapies for NDs provide primarily symptomatic relief and have a limited impact on disease progression. Considering the high global prevalence and economic burden of these disorders, the identification of effective and well-tolerated therapeutic alternatives is an urgent priority. Therefore, this review synthesizes current evidence on the pharmacological actions of antidiabetic agents in neurodegenerative disorders and highlights implications for future experimental and clinical investigations. To support this objective, a comprehensive literature search was performed across PubMed, ScienceDirect, Web of Science, and ClinicalTrials.gov to retrieve relevant interventional and translational studies. Data extraction, processing, and visualization were performed using Python-based computational workflows to systematically map research trends, drug classes, and mechanistic overlaps.

SHARED PATHOPHYSIOLOGICAL MECHANISMS LINKING T2DM AND NDs

T2DM and NDs share multiple convergent molecular and cellular mechanisms leading to impaired neuronal homeostasis and declining cognitive performance. The key interconnected pathways underlying this relationship are outlined below.

Brain insulin resistance and glucose metabolism impairment

Brain insulin resistance constitutes a pivotal pathophysiological intersection between NDs and T2DM. Insulin plays a crucial role in neuronal survival, synaptic plasticity, and glucose uptake by activating the PI3K/AKT and MAPK/ERK signaling cascades (Andrade et al., 2024; Carvalho & Moreira, 2023; Dai et al., 2023). Impaired insulin signaling diminishes AKT phosphorylation and activates GSK-3β, which in turn promotes β-amyloid (Aβ) accumulation and tau hyperphosphorylation (Andrade et al., 2024; Kciuk et al., 2024). In PD, reduced expression of GLUT3 and GLUT4 transporters within dopaminergic neurons limits glucose uptake, resulting in ATP depletion and α-synuclein aggregation (Dai et al., 2023; Sabari et al., 2023; Tanvir et al., 2024). Collectively, these alterations impair neuronal energy metabolism, exacerbate protein aggregation, and contribute to progressive synaptic loss and cognitive deterioration.

Mitochondrial dysfunction and energy metabolism deficits

Among the shared mechanisms between DM and NDs, mitochondrial impairment is increasingly recognized as a key driver of neuronal damage. Hyperglycemia and insulin resistance suppress mitochondrial respiratory chain complexes I and III, which leads to reduced ATP synthesis and increased reactive oxygen species (ROS) generation (Carvalho & Moreira, 2023; Veselov et al., 2023). This process leads to cytochrome c release and apoptotic signaling cascades. Dopaminergic neurons in PD are particularly vulnerable to mitochondrial stress and energy deficits, which promote neuronal death and α-synuclein aggregation (Dai et al., 2023; Sabari et al., 2023). Pharmacologically, metformin and several GLP-1 receptor agonists (GLP-1 RAs) promote AMPK signaling, support mitochondrial biogenesis, and enhance neuronal energy metabolism, thereby improving both glucose homeostasis and neuronal resilience (Mohammed & Kelemu, 2025; Reed et al., 2025).

Oxidative stress and redox imbalance

Chronic hyperglycemia and insulin resistance increase excessive ROS production from NADPH oxidases and mitochondrial sources, intensifying oxidative stress in neuronal tissue (Li et al., 2023; Veselov et al., 2023). This redox imbalance accelerates lipid peroxidation, protein carbonylation, and DNA damage while fostering Aβ and α-synuclein accumulation (Ghosh et al., 2023; Veselov et al., 2023). Antidiabetic agents such as GLP-1 RAs, DPP-4 inhibitors, and metformin counteract these effects by activating the Nrf2/ARE pathway, enhancing the transcription of endogenous antioxidant enzymes (SOD, CAT, GPx), and thereby exerting robust neuroprotective actions (Ghosh et al., 2023; Ibrahim et al., 2025; Mohammed & Kelemu, 2025; Reed et al., 2025).

Amyloid and protein aggregation

Insulin resistance and oxidative stress disrupt protein homeostasis, thereby accelerating neurodegenerative cascades. Dysregulated insulin signaling alters amyloid precursor protein (APP) processing, facilitating Aβ overproduction and tau hyperphosphorylation (Andrade et al., 2024; Kciuk et al., 2024). In PD, mitochondrial dysfunction and ROS accumulation foster α-synuclein misfolding and oligomerization (Dai et al., 2023; Sabari et al., 2023). GLP-1 RAs and DPP-4 inhibitors mitigate these effects by enhancing autophagy and proteasomal degradation, thereby reducing toxic protein aggregates (Ibrahim et al., 2025; Mohammed & Kelemu, 2025; Sulangi et al., 2024; Złotek et al., 2023).

Neuroinflammation and microglial activation

Prolonged hyperglycemic states stimulate inflammatory signaling pathways, increasing the release of cytokines, including TNF-α, IL-1β, and IL-6, and thereby facilitating microglial reactivity and neuroinflammatory cascades (Li et al., 2023; Yu et al., 2025). This sustained inflammatory milieu contributes to synaptic impairment and neuronal apoptosis. Metformin and GLP-1 RAs attenuate these processes by suppressing NF-κB and JNK signaling cascades, shifting microglial polarization toward an anti-inflammatory M2 phenotype, and ultimately conferring neuroprotection in both AD and PD models (Ibrahim et al., 2025; Mohammed & Kelemu, 2025; Reed et al., 2025).

Autophagy and proteostasis dysregulation

Defective autophagic clearance represents another critical mechanism linking T2DM and NDs. Hyperglycemia and insulin resistance impair autophagic flux, leading to the accumulation of misfolded Aβ and α-synuclein species. GLP-1 RAs and DPP-4 inhibitors restore autophagic function through modulation of AMPK and mTOR, enhancing lysosomal biogenesis and promoting neuronal proteostasis (Ibrahim et al., 2025; Luo et al., 2025; Złotek et al., 2023). These effects may slow cognitive decline and neuronal loss in diabetic and neurodegenerative contexts.

Glucose metabolism and neuronal energy imbalance

Disturbances in cerebral glucose metabolism lead to neuronal energy depletion and lactate accumulation (Dai et al., 2023; Dou et al., 2025; Kan et al., 2025). Reduced expression of GLUT1 and GLUT3 transporters diminishes glucose uptake and ATP production, impairing synaptic efficacy. GLP-1 RAs and SGLT2 inhibitors improve cerebral glucose utilization, stabilize energy metabolism, and ameliorate synaptic dysfunction (Dou et al., 2025; Ibrahim et al., 2025; Złotek et al., 2023).

Incretin system and neuroprotection

Beyond glycemic regulation, incretin-based therapies exhibit pleiotropic neuroprotective properties. GLP-1 RAs and DPP-4 inhibitors activate PI3K/AKT and AMPK pathways, enhance synaptic plasticity, attenuate oxidative stress, suppress NF-κB-driven inflammation, and promote autophagy (Ibrahim et al., 2025; Koshatwar et al., 2023; Nowell et al., 2023; Pandiyan et al., 2024; Sulangi et al., 2024). Consequently, these agents reduce Aβ and α-synuclein burden, preserve neuronal energy homeostasis, and mitigate cognitive decline in both AD and PD.

Taken together, these overlapping mechanisms highlight the multifaceted neuroprotective potential of antidiabetic agents. As summarized in table 1, these drugs target several interconnected neurodegenerative pathways, including insulin resistance, disruptions in mitochondrial homeostasis, increased oxidative burden, pathological protein misfolding, neuroimmune activation, impaired autophagy, and altered glucose metabolism. By modulating these mechanisms, antidiabetic agents may not only restore metabolic balance but also mitigate neuronal injury and cognitive decline, providing a promising avenue for therapeutic repurposing in neurodegenerative disorders.

Table 1. Shared pathophysiological mechanisms and the impact of antidiabetic agents

Primary Pathophysiological Category	Pathophysiological Mechanism	Key Molecular/Cellular Outcomes	Associated Antidiabetic Agents
Insulin and Glucose Regulation	Brain insulin resistance	Increased Aβ deposition, tau hyperphosphorylation and reduced bioenergetics	Metformin, GLP-1 RAs
Cellular Energy Metabolism	Mitochondrial dysfunction	Decreased ATP production, elevated ROS and enhanced apoptosis	Metformin, GLP-1 RAs
Oxidative Balance	Oxidative stress	Lipid peroxidation, protein carbonylation and DNA damage	GLP-1 RAs, DPP-4 inhibitors, Metformin
Protein Aggregation	Amyloid and protein aggregation	Accumulation of Aβ and α-synuclein	DPP-4 inhibitors, GLP-1 RAs
Proteostasis and Autophagy	Autophagy impairment	Accumulation of toxic proteins, disrupted homeostasis	GLP-1 RAs, DPP-4 inhibitors
Neuroinflammation	Microglial activation	Increased proinflammatory cytokines (TNF-α, IL-6, IL-1β)	Metformin, GLP-1 RAs
Glucose and Energy Metabolism	Glucose metabolism impairment	Reduced ATP synthesis and impaired synaptic function	GLP-1 RAs, SGLT2 inhibitors
Incretin-mediated Neuroprotection	Incretin signaling	Enhanced synaptic plasticity, decreased ROS, improved autophagy	GLP-1 RAs, DPP-4 inhibitors

REPURPOSING POTENTIAL OF ANTIDIABETIC DRUGS FOR THE MANAGEMENT OF NDs

Given the emerging overlap between T2DM and NDs, several antidiabetic drug classes have been evaluated for their neuroprotective potential. The following sections synthesize pivotal evidence regarding the repurposing potential of these agents, focusing on both mechanistic insights and clinical outcomes.

Biguanides

Biguanide agents, metformin being the main example, are widely prescribed for the treatment of T2DM. The presence of shared pathophysiological pathways between DM and NDs, including chronic hyperglycemia, insulin resistance, oxidative stress, and neuroinflammatory processes, supports the potential neurological repurposing of these agents. In a post-mortem cohort study conducted by Barthold et al. (2021), individuals with diabetes who had used metformin for at least five years exhibited a significant reduction in cortical Aβ1-42 levels, suggesting a possible protective effect against AD-specific pathology. However, analyses of established AD neuropathological parameters, including plaque load, tangle distribution, and CERAD classification, revealed no measurable differences. Mechanistically, Cai et al. (2020) demonstrated that metformin modulates unfolded protein response (UPR) pathways via AMPK/ERK1/2 signaling, contributing to proteostasis maintenance and regulating intracellular energy balance, mitochondrial function, and cell survival. Papini et

al. (2024) suggested that metformin may also exert effects through lysosome-dependent mechanisms, activating AMPK via lysosomal targets and modulating autophagy and lysosomal function. Additionally, Campagnoli et al. (2025) summarized the pleiotropic actions of metformin, highlighting its ability to influence neurodegenerative processes through both lysosomal/autophagy pathways and metabolic signaling. Collectively, these findings suggest that metformin has the potential to affect specific neurodegenerative biomarkers, particularly Aβ1-42, although its impact may not be consistent across to all AD pathological endpoints. Consequently, while the repurposing of metformin and related biguanides for AD and other neurodegenerative processes appears promising, further well-designed randomized controlled trials are required to establish optimal dosing, treatment duration, patient selection, and safety-efficacy profiles.

Thiazolidinediones (TZDs)

Thiazolidinediones (TZDs) are an oral antidiabetic drug class that enhances insulin sensitivity in T2DM management. The presence of shared pathophysiological pathways between DM and NDs (particularly insulin resistance, chronic inflammation, mitochondrial dysfunction, and oxidative stress) supports their potential neurological repurposing. A prospective observational study based on the U.S. Veterans Affairs database, including T2DM patients aged ≥60 years, reported that individuals receiving TZD monotherapy had approximately a 22% lower risk of all-cause dementia compared to those on metformin monotherapy. In contrast, sulfonylurea monotherapy was associated with an approximately 12% increased dementia risk relative to metformin (Tang et al., 2022). These findings suggest that TZDs may exert neuroprotective effects at the central nervous system level, beyond their glucose-lowering properties. Mechanistically, studies have shown that PPARγ agonists (e.g., glitazones) can modulate processes related to neurodegeneration, including mitochondrial redox balance, oxidative stress, neuroinflammation, proteasomal activity and pathological protein accumulation, as well as cellular energy metabolism (Durai et al., 2022). In particular, Alhowail et al. (2022) reviewed evidence indicating that pioglitazone can exert neuroprotective effects by regulating inflammatory cytokines (IL-1, IL-6, TNF-α) and NF-κB/p38 MAPK signaling pathways, while ameliorating oxidative stress and mitochondrial dysfunction. In an *in vitro* neuronal culture model, troglitazone was shown to enhance PPARγ activation and modulate autophagic flux, preventing neuronal cell death induced by prion peptides (Moon et al., 2021). Additionally, in a chronic repetitive mild traumatic brain injury model, PPARγ activation reduced microglial activation, prevented learning and memory deficits, and regulated signaling pathways including NLRP3 inflammasome, STAT3, and NF-κB (Pearson et al., 2024). Taken together, these findings from clinical observational, molecular mechanistic, and in vitro/preclinical studies highlight TZDs as a promising candidate for repurposing in the prevention or slowing of progression of neurodegenerative disorders such as AD and vascular dementia. However, because most of the available evidence is observational or preclinical, causal inferences are limited. Further clinical studies are needed.

GLP-1 receptor agonists (GLP-1 RAs)

GLP-1 RAs are widely used in the treatment of T2DM and are effective in both glycemic control and weight reduction. This class includes agents such as liraglutide, semaglutide, dulaglutide, and exenatide (Yao et al., 2024). The presence and functional significance of GLP-1 RAs in the human brain play a central role in the link between T2DM and NDs. Animal models have demonstrated that GLP-1 RAs are essential for learning and memory processes, with receptor deficiency leads to impairments in spatial memory and neuronal survival (During et al., 2003). Notably, GLP-1 receptors are primarily expressed in neurons but not in glial cells, suggesting that GLP-1 exerts its central nervous system effects directly at synaptic and neuronal levels (Hamilton & Hölscher, 2009).

Evidence from human studies indicates that GLP-1 receptors are expressed in several brain regions, including the parietal cortex, hypothalamus, and medulla. Moreover, liraglutide administration in individuals with T2DM has been associated with reduced neural responses to highly palatable food stimuli (Farr et al., 2016). Among neurodegenerative disorders, PD has received the most attention, as GLP-1 RAs have been shown to reduce dopaminergic neuronal loss, support mitochondrial function, and suppress oxidative stress and neuroinflammation (Kalinderi et al., 2024). These agents improve neuronal insulin signaling, reduce brain insulin resistance, enhance mitochondrial ATP production, decrease pro-inflammatory cytokines, promote synaptic growth, elevate neurotrophic factors (BDNF, GDNF), modulate protein aggregation (Aβ, tau), and maintain the stability of the blood–brain barrier and neurovascular unit (Kalinderi et al., 2024; Kopp et al., 2022). Meta-analyses indicate that GLP-1 RAs can improve motor function in PD, although effects vary and adverse effects are possible (Helal et al., 2025; Kopp et al., 2022). Conversely, in ALS mouse models, GLP-1 RAs such as liraglutide have not demonstrated a slowing of disease progression (Keerie et al., 2021). Collectively, these findings demonstrate that GLP-1 RAs not only regulate glucose homeostasis but also influence neurodegenerative processes through multiple mechanisms, including insulin signaling, mitochondrial function, oxidative stress, neuroinflammation, proteostasis, synaptic plasticity, and blood-brain barrier preservation.

Sodium-glucose cotransporter-2 (SGLT2) inhibitors

Emerging evidence indicates that SGLT2 inhibitors may help maintain cognitive performance by modulating oxidative stress-related processes within the central nervous system (e.g., activation of NADPH oxidase subunits, superoxide production, 8-hydroxydeoxyguanosine levels), suppressing neuroinflammation (e.g., glial cell reactivity accompanied by increased release of inflammatory mediators), maintaining blood-brain barrier integrity, preventing amyloid-β accumulation and tau hyperphosphorylation, ameliorating mitochondrial dysfunction (e.g., increased ROS, loss of membrane potential), enhancing synaptic plasticity and neurotrophic factor expression (e.g., BDNF), and improving cerebral glucose utilization (Mei et al., 2024; Shin et al., 2024). In a recent retrospective cohort study of patients with T2DM aged 60 years or over found that, those treated with SGLT2 inhibitors had a 20% lower incidence of dementia (Sarabhai et al., 2025). A meta-analysis of eight cohort studies involving 1,275,257 participants indicated that SGLT2 inhibitor use was associated with approximately 33% lower risk of all-cause dementia compared to DPP-4 inhibitors (Mei et al., 2024). Furthermore, a pharmacodynamic-based multicenter network meta-analysis evaluating the preventive potential of SGLT2 inhibitors and GLP-1 RAs against NDs reported that only dapagliflozin showed a significant protective effect against PD (OR = 0.28, 95% CI 0.09–0.93) (Tseng et al., 2025). This effect has been attributed to dapagliflozin's high SGLT2 selectivity and anti-inflammatory properties, which may reduce dopaminergic neuron loss and suppress neuroinflammation. Other SGLT2 inhibitors (e.g., empagliflozin, canagliflozin) and GLP-1 RAs (e.g., liraglutide, semaglutide) did not demonstrate significant effects, likely due to methodological and biological factors such as insufficient follow-up duration, lack of neurological endpoints, pharmacodynamic variability, and limited sample sizes (Tseng et al., 2025). Nevertheless, clinical evidence remains limited, and long-term safety profiles, efficacy in non-diabetic populations, and the role of combination therapies warrant further investigation.

Dipeptidyl peptidase-4 (DPP-4) inhibitors

DPP-4 inhibitors possess significant potential for reducing the risk of NDs, consciousness impairment, and cognitive dysfunction in individuals with T2DM. Clinical cohort analyses have demonstrated that treatment with DPP-4 inhibitors among diabetic

patients is associated with a significant reduction in neurological morbidity compared to other oral antidiabetic agents (Brauer et al., 2020; Lin et al., 2023). Moreover, a deep learning-based drug screening study combined with retrospective clinical analysis suggested that saxagliptin may have a beneficial effect in long-term cases of consciousness impairment. DPP-4 inhibition elevates endogenous GLP-1 and GIP levels, thereby reactivating neuronal insulin/IGF-1 signaling, suppressing neuroinflammation, oxidative stress, and tau/amyloid-β pathology, and supporting monoaminergic and GABAergic neurotransmission (Toker et al., 2025). Systematic review and meta-analysis data further indicate that DPP-4 inhibitors have a positive effects on the cognitive function of patients with T2DM, as evidenced by improvements in MMSE and IADL scores (Meng et al., 2023). Collectively, these findings increasingly suggest that DPP-4 inhibitors may serve as neuroprotective agents in modulating diabetes-associated cognitive dysfunction (Sulangi et al., 2024).

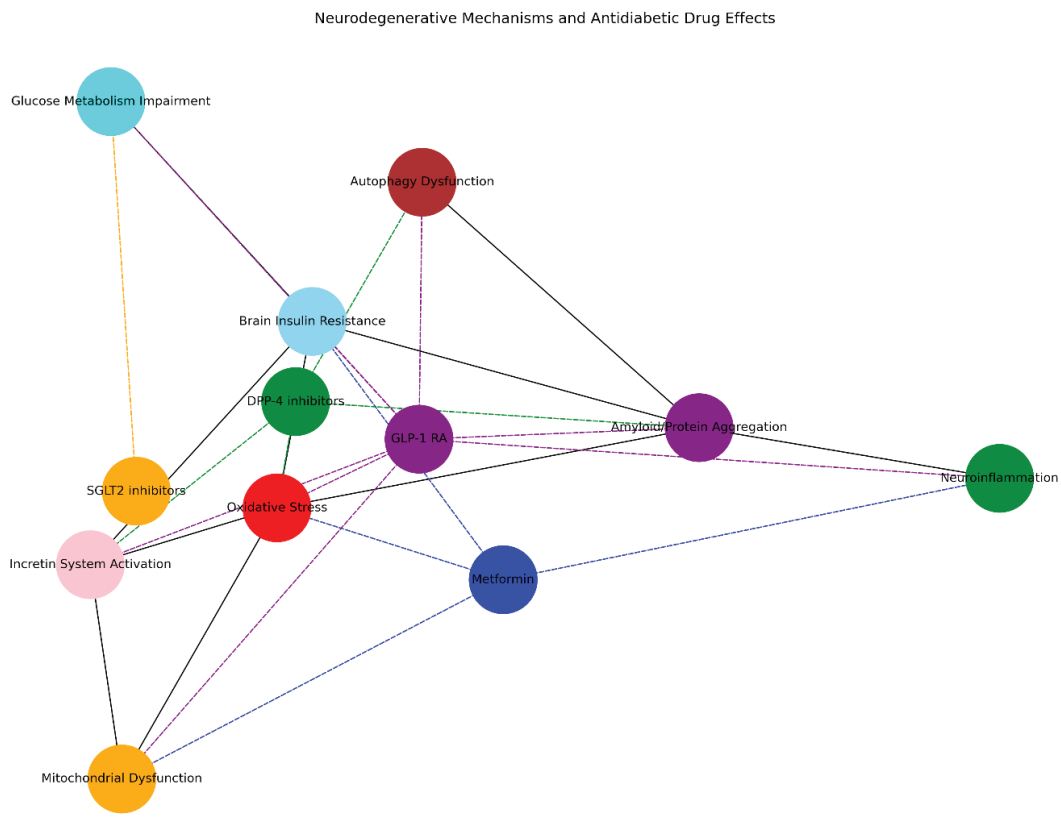

Figure 1. Pathways of neurodegeneration and the therapeutic targets of antidiabetic drugs

Figure 1 presents a color-coded network visualization of the pathways of neurodegeneration and the therapeutic targets of antidiabetic drugs. Solid black arrows represent established mechanistic interactions between pathological processes, while dashed colored lines indicate the modulatory effects of specific drug classes. Nodes are categorized by functional domain: brain insulin resistance (skyblue), glucose metabolism impairment (cyan), mitochondrial dysfunction (orange), oxidative stress (red), amyloid/protein aggregation (purple), neuroinflammation (dark green), autophagy dysfunction (brown), and incretin system activation (pink). Drug nodes (Metformin, GLP-1 RA, DPP-4 inhibitors, and SGLT2 inhibitors) are positioned centrally to demonstrate their pleiotropic impact across multiple neuroprotective axes.

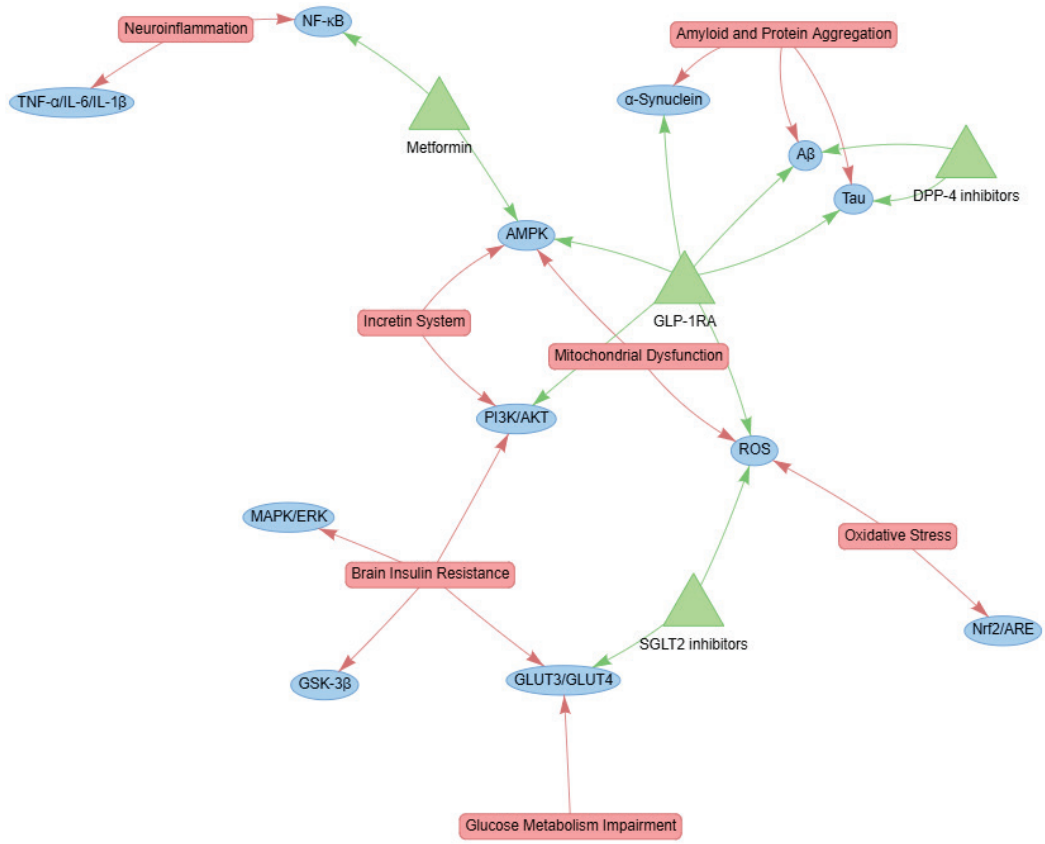

Figure 2. Therapeutic network of antidiabetic drugs targeting pathophysiological links between T2DM and NDs

Figure 2 illustrates a mechanistic network highlighting the key pathophysiological mechanisms linking T2DM with NDs. Nodes represent major processes -including brain insulin resistance, mitochondrial dysfunction, oxidative stress, neuroinflammation, glucose metabolism disturbance, and protein aggregation- as well as associated molecular pathways and proteins such as PI3K/AKT, MAPK/ERK, GSK-3β, GLUT3/GLUT4, AMPK, ROS, Nrf2/ARE, TNF-α/IL-6/IL-1β, NF-κB, Aβ, tau, and α-synuclein. Pharmacological agents (metformin, GLP-1 RAs, DPP-4 inhibitors, and SGLT2 inhibitors) are also represented. Edges indicate mechanistic or regulatory relationships, including activation, inhibition, upregulation, downregulation, hyperphosphorylation, or aggregation. The network demonstrates how insulin resistance activates GSK-3β and reduces GLUT3/GLUT4 expression, thereby promoting protein aggregation and impairing neuronal glucose uptake, while antidiabetic agents modulate these pathways to exert neuroprotective effects.

SUMMARY OF INTERVENTIONAL STUDIES ON ANTIDIABETIC AGENTS IN NEURODEGENERATIVE DISORDERS

A systematic search of the ClinicalTrials.gov database was conducted to identify interventional trials investigating the therapeutic potential of antidiabetic agents in NDs up to October 31, 2025.

The search strategy included the following keywords in the *Intervention/Treatment* field:

"metformin" OR "pioglitazone" OR "rosiglitazone" OR "liraglutide" OR "exenatide" OR "semaglutide" OR "lixisenatide" OR "dulaglutide" OR "sitagliptin" OR "vildagliptin" OR "empagliflozin" OR "dapagliflozin" OR "canagliflozin" OR "insulin".

Inclusion criteria encompassed interventional studies targeting AD, PD, ALS, HD, or other NDs, in which the aforementioned antidiabetic agents were used as primary or adjunctive interventions. Data extraction focused the study phase, status, target condition, intervention, and mechanistic information reported in the trial summaries. Frequencies of interventions and molecular pathways were tabulated to provide a quantitative overview of the current clinical landscape.

The analysis of 76 included trials reveals that the majority of trials are in early to intermediate phases (Phase I-II), with fewer progressing to late-phase studies (Phase III-IV) (Figure 3.). Disease distribution highlights a predominant focus on PD and AD, with other significant conditions including MS and trials focusing on (ALS) (Figure 5.), while examination of study status indicates that a substantial number of trials are still ongoing or recruiting, and that the largest proportion of trials has been completed (Figure 4.). From a pharmacological standpoint, the most frequently investigated interventions are GLP-1 RAs, DPP-4 inhibitors, SGLT2 inhibitors, and metformin (Figure 6.). Mechanistic information extracted directly from trial summaries includes modulation of insulin signaling, attenuation of neuroinflammation, reduction of oxidative stress, enhancement of mitochondrial function, and regulation of autophagy, with less frequently reported mechanisms include reduction of endoplasmic reticulum stress, neurotrophic signaling, and anti-apoptotic pathways. These findings provide direct evidence of the molecular targets actively pursued in clinical investigations of metabolic modulators for neurodegenerative disorders.

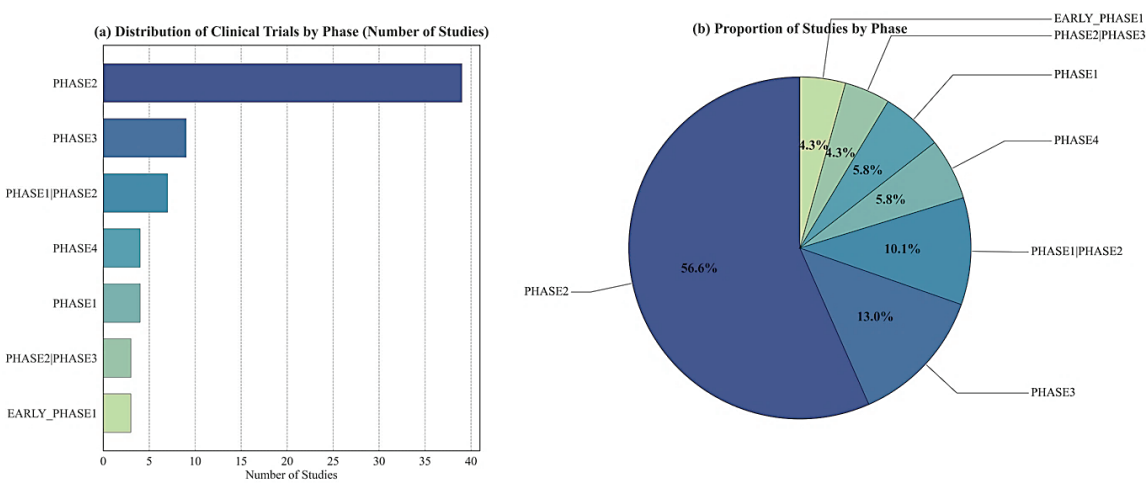

Figure 3. Numerical (a) and proportional (b) distribution of clinical trials by phase.

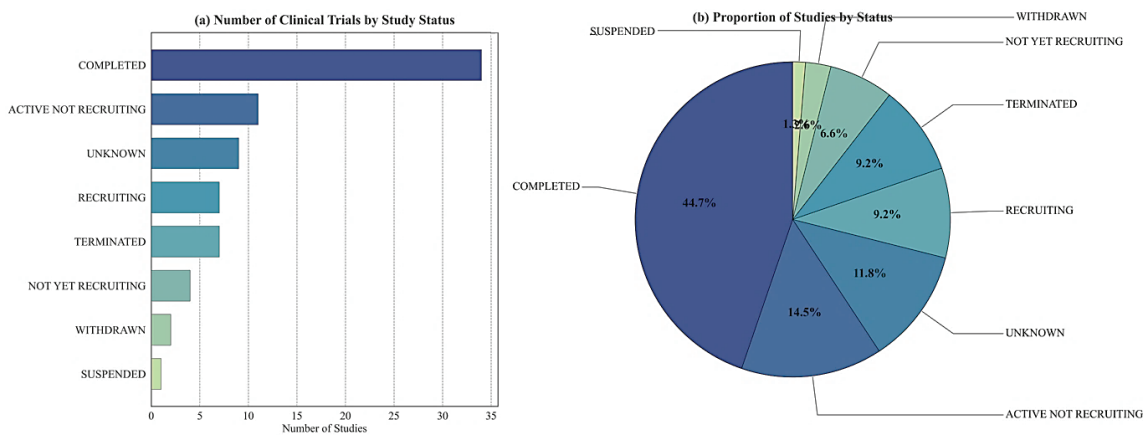

Figure 4. Numerical (a) and proportional (b) distribution of clinical trials by study status. (*COMPLETED*: study finished; *ACTIVE, NOT RECRUITING*: ongoing, no new enrollment; *UNKNOWN*: status not recently updated; *RECRUITING*: open for enrollment; *TERMINATED*: stopped early; *NOT YET RECRUITING*: registered but not started; *WITHDRAWN*: cancelled before enrollment; *SUSPENDED*: temporarily halted).

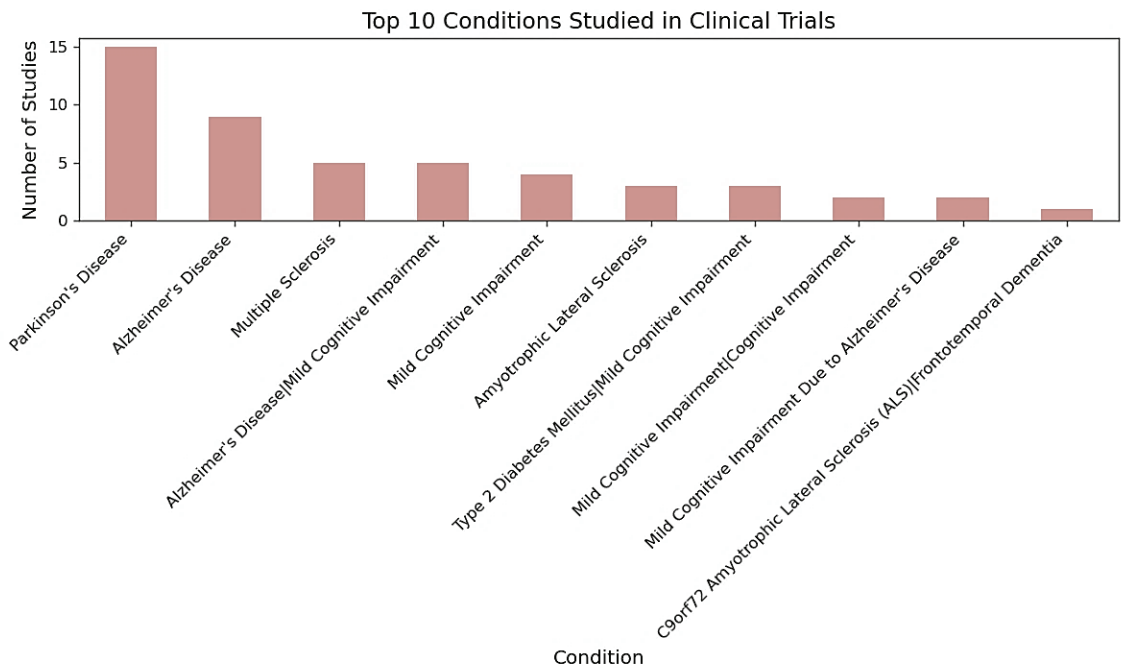

Figure 5. Top 10 conditions studied in clinical trials.

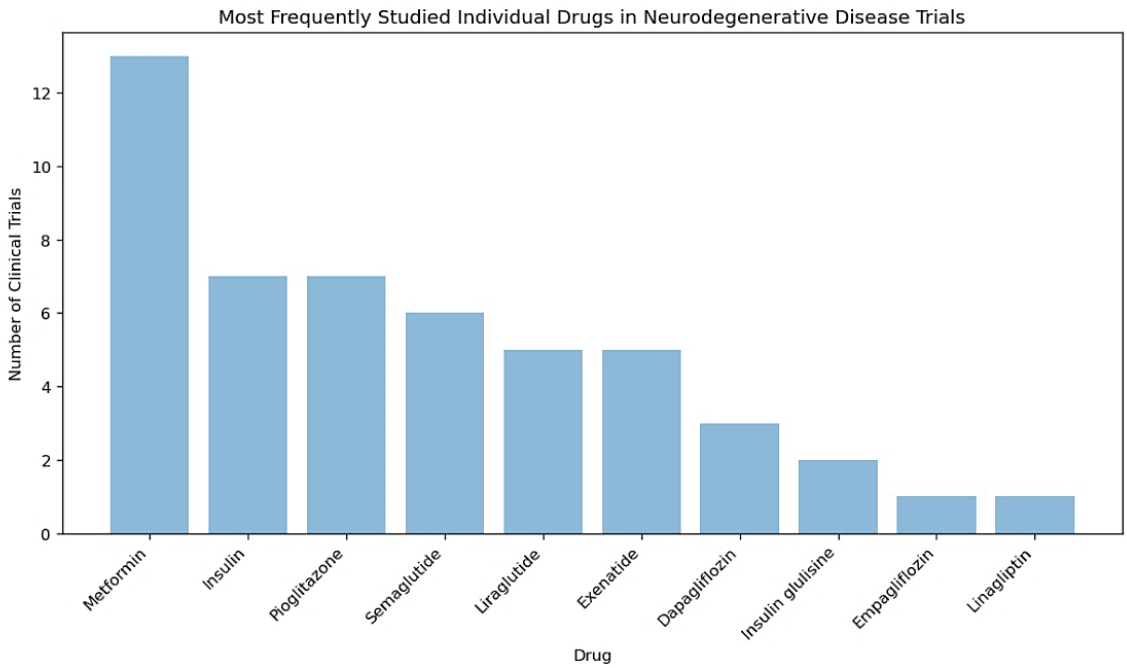

Figure 6. Most frequently studied antidiabetic drugs in NDs trials.

Antidiabetic and metabolically active agents evaluated in clinical trials for NDs demonstrate heterogeneous efficacy across drug classes and disease indications. To address the availability of outcome data from completed studies, the main clinical findings of eligible trials are summarized in table 2, providing a structured overview of reported efficacy and safety results. Although a substantial proportion of trials remain ongoing or in early phases, analysis of completed studies offers important insights into clinical outcomes. Several completed trials did not report publicly available outcomes, highlighting that trial completion alone does not necessarily indicate clinical benefit and should be interpreted cautiously (Santiago et al., 2023). Among agents with reported results, GLP-1 receptor agonists and related compounds showed the most consistent signals of potential benefit; exenatide improved off-medication motor scores in PD (Athauda et al., 2017) and lixisenatide reduced progression of motor disability (Meissner et al., 2024), while liraglutide prevented decline in cerebral glucose metabolism despite limited cognitive effects (Gejl et al., 2016). Intranasal insulin demonstrated improvements in verbal fluency, cognitive performance, and white matter hyperintensity progression in selected populations (Kellar et al., 2021; Novak et al., 2019), and multi-target metabolic interventions were associated with improvements in cognition and biomarker profiles (Erichsen et al., 2025). In contrast, several trials reported neutral or negative efficacy findings, including futility results for pioglitazone in early PD (NINDS Exploratory Trials in Parkinson Disease Investigators, 2015) and lack of significant clinical benefit with metformin or NLY01 in specific populations (Abdelgaied et al., 2026; McGarry et al., 2024). Mechanistic and biomarker-focused studies identified proteomic and metabolic alterations without clear short-term clinical improvement (Weinberg et al., 2024). Importantly, across studies, antidiabetic agents were generally well tolerated with acceptable safety profiles, supporting continued investigation despite variable efficacy outcomes (Athauda et al., 2017; Erichsen et al., 2025; McGarry et al., 2024; Meissner et al., 2024).

Table 2. Clinical outcomes and safety profiles of completed clinical trials evaluating antidiabetic and metabolically active agents in NDs

NCT	Disease	Intervention	Main Clinical Outcome	Overall Interpretation	Safety
NCT05081219 (Erichsen et al., 2025)	MCI and early AD	Combination therapy (intranasal insulin, empagliflozin)	Improved cognitive performance and modulated fluid biomarkers of neurodegeneration.	Positive signal	Well tolerated
NCT01965756 (Weinberg et al., 2024)	MCI related to AD	Metformin	Significant alterations in multiple plasma and cerebrospinal fluid protein levels.	Biomarker signal only	NR
NCT06812585 (Abdelgaied et al., 2026)	Relapse-remitting MS	Metformin (as an add-on therapy to IFNβ-1a)	No significant improvement in neurodegeneration biomarkers or clinical outcomes.	Neutral outcome	Well tolerated
NCT01971242 (Athauda et al., 2017)	PD	Exenatide	Significant improvement in off-medication motor scores sustained through the washout period.	Positive signal	Well tolerated
NCT01469351 (Gejl et al.,, 2016)	AD	Liraglutide	Prevented decline in cerebral glucose metabolism without altering amyloid or cognition.	Biomarker signal only	NR
NCT01767909 (Kellar et al., 2021)	MCI or AD	Intranasal insulin	Reduced white matter hyperintensity progression associated with improved cognitive function.	Positive signal	NR
NCT01280123 (NINDS Exploratory Trials in Parkinson Disease Investigators, 2015)	Early PD	Pioglitazone	No significant difference in motor score progression compared to placebo.	Negative or Futility	Well tolerated
NCT02064166 (Novak et al., 2019)	PD and MSA	Intranasal insulin	Functional improvement in verbal fluency and standardized motor performance scores.	Positive signal	Well tolerated
NCT04154072 (McGarry et al., 2024)	Early untreated PD	NLY01 (A brain-penetrant, pegylated, longer-lasting version of exenatide)	No significant improvement in motor or non-motor features versus placebo.	Neutral outcome	Well tolerated
NCT03439943 (Meissner et al., 2024)	Early PD	Lixisenatide	Significantly less progression of motor disbility compared to placebo.	Positive signal	Adverse events notable

NCT: National Clinical Trial identifier, NR: Not reported, MCI: Mild Cognitive Impairment, MSA: Multiple System Atrophy

CONCLUSIONS

The growing global burden of NDs, driven by population aging and increased life expectancy, continues to pose a major challenge to public health. Conventional therapeutic approaches have largely failed to halt or reverse neurodegenerative progression, underscoring the urgent need for novel, disease-modifying strategies. Within this context, the pharmacological

repurposing of antidiabetic agents has emerged as a promising and cost-effective approach. These compounds, characterized by well-established pharmacokinetic and safety profiles, offer the opportunity to bypass the prolonged and costly process of de novo drug development while providing mechanistic plausibility through their modulation of shared metabolic and neurodegenerative pathways.

Accumulating preclinical and clinical evidence suggests that antidiabetic agents, such as GLP-1 RAs, DPP-4 inhibitors, SGLT-2 inhibitors, metformin and insülin, have multifaceted neuroprotective actions. Their effects extend beyond glycemic regulation to include the modulation of central insulin signaling, attenuation of oxidative stress and mitochondrial dysfunction, suppression of neuroinflammatory and apoptotic cascades, and restoration of synaptic and autophagic homeostasis. By targeting convergent molecular networks implicated in both T2DM and NDs, these metabolic agents hold potential for disease-modifying efficacy rather than merely providing symptomatic relief. However, despite encouraging findings, substantial translational gaps persist. Clinical evidence remains fragmented, with inconsistent reporting of long-term cognitive and functional outcomes, and a lack of mechanistic biomarkers in clinical trial protocols. Furthermore, heterogeneity in study design, patient selection, and outcome measures continues to hinder comparative evaluation across drug classes.

Future research should prioritize biomarker-driven, mechanism-targeted clinical trials integrating neuroimaging, molecular, and electrophysiological endpoints to clarify therapeutic mechanisms. Harmonization of neurocognitive assessment tools and the inclusion of early-intervention paradigms -particularly at prodromal or preclinical stages- may further enhance translational validity. Moreover, multi-omics approaches and systems pharmacology modeling offer promising tools for delineating network-level drug effects and identifying novel metabolic targets within the neurodegenerative cascade. By systematically integrating mechanistic and clinical trial data, this review provides a unique translational framework for understanding how metabolic modulation may be leveraged in the prevention and treatment of NDs. Ultimately, incorporating metabolic therapeutics into the broader neuropharmacological framework may not only advance our understanding of the shared pathophysiology between DM and NDs but also pave the way toward accessible, mechanism-informed interventions capable of altering disease trajectories.

AUTHOR CONTRIBUTION STATEMENT

Concept (AHB), design (AHB), literature search (AHB), data processing (AHB), writing (AHB), interpretation (AHB), critical reviews (AHB).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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