RESEARCH PAPER

Beyond Glycemic Control: Neuroprotective Effects of Antidiabetic Drugs in Alzheimer's Disease

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ABSTRACT

Background: Alzheimer's disease (AD) and type 2 diabetes mellitus (T2DM) share mechanistically overlapping pathways, including central insulin resistance, neuroinflammation, oxidative stress, and aberrant protein aggregation. This convergence, encapsulated in the concept of "Type 3 Diabetes," has generated interest in repurposing antidiabetic drugs as neuroprotective agents.

Objective: This systematic review critically evaluates the neuroprotective evidence for five major antidiabetic drug classes: metformin, GLP-1 receptor agonists, DPP-4 inhibitors, thiazolidinediones, and insulin (including intranasal delivery) across preclinical and clinical AD research.

Methods: A structured literature search was conducted across PubMed, Scopus, Web of Science, and ClinicalTrials.gov for studies published between January 2019 and December 2024. Relevant Boolean search terms related to AD, T2DM, insulin resistance, and antidiabetic drugs were applied. Eligible studies were selected using predefined criteria. PRISMA 2020 guidelines were followed throughout.

Results: Preclinical evidence across transgenic and streptozotocin-induced AD models consistently demonstrates reductions in amyloid-β burden, tau hyperphosphorylation, microglial activation, and oxidative stress following antidiabetic drug administration. GLP-1 receptor agonists and intranasal insulin show the most clinically translatable signals. Metformin demonstrates broad neuroprotective mechanisms but faces blood-brain barrier limitations. DPP-4 inhibitors and thiazolidinediones provide anti-inflammatory benefit with mixed or limited clinical evidence. Completed clinical trials have been largely underpowered, heterogeneous, and insufficiently biomarker-stratified, limiting definitive conclusions.

Conclusion: Antidiabetic drugs represent a pharmacologically rational strategy for AD therapeutics, particularly in individuals with comorbid insulin resistance. Biomarker-enriched, adequately powered, pharmacogenomically stratified clinical trials remain the critical next step toward translating preclinical signals into clinical benefit

Keywords: Alzheimer's disease; type 2 diabetes mellitus; insulin resistance; GLP-1 receptor agonists; metformin; neuroprotection; drug repurposing; neuroinflammation; amyloid-beta; tau pathology; intranasal insulin; PPAR-γ

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INTRODUCTION

1.1 Global Burden of T2DM and Alzheimer's Disease

Type 2 diabetes mellitus and Alzheimer's disease stand among the most pressing chronic disease burdens of the current century. Both conditions are driven by population aging, sedentary lifestyles, and urbanization, and they are projected to escalate substantially over the coming decades. The International Diabetes Federation estimated that 537 million adults were living with diabetes globally in 2021, a

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figure forecast to reach 783 million by 2045 [1]. Alzheimer's disease, responsible for 60–70% of all dementia cases, affects approximately 55 million individuals worldwide, with new diagnoses occurring at a rate of nearly 10 million per year [2]. Beyond their individual burdens, the two conditions increasingly co-occur. Older adults with T2DM have a higher risk of cognitive decline, and this is important for healthcare. Annual global costs attributable to dementia exceeded USD 1.3 trillion in 2019 and are projected to approach USD 2.8 trillion by 2030 [2]. The cost of managing T2DM complications, including neurological sequelae, compounds this burden. Understanding the biological links between the two conditions is therefore not only scientifically urgent but clinically and economically necessary.

1.2 Epidemiological Overlap Between Diabetes and Dementia

Epidemiological data establish a consistent association between T2DM and elevated AD risk. A meta-analysis of 144 prospective cohort studies found that individuals with T2DM carried approximately a 1.5- to 2-fold greater risk of developing dementia, with the association persisting after adjustment for vascular risk factors [3]. Longitudinal analyses from the UK Biobank corroborate accelerated hippocampal atrophy and white matter lesion burden in individuals with T2DM, even before overt cognitive impairment manifests [4]. The relationship is not straightforwardly causal. Shared upstream risk factors, including obesity, physical inactivity, hypertension, dyslipidemia, and chronic low-grade inflammation, contribute to both conditions. However, mechanistic evidence supports direct biological pathways beyond shared etiology. Hyperinsulinemia, for instance, competes with amyloid-β (Aβ) for degradation by insulin-degrading enzyme (IDE), reducing cerebral Aβ clearance and accelerating plaque accumulation [5]. This IDE-mediated link exemplifies how peripheral metabolic dysfunction directly modifies central neuropathology.

1.3 The Concept of "Type 3 Diabetes" Brain Insulin Resistance

The term "type 3 diabetes" was proposed to describe a neurodegeneration-associated state of brain-specific insulin resistance [6]. The designation reflects the observation that AD brains exhibit markedly impaired insulin signaling, reduced insulin receptor expression, attenuated PI3K/Akt pathway activity, and increased serine phosphorylation of insulin receptor substrate-1 (IRS-1) features that parallel peripheral insulin resistance in T2DM but occur in the absence of systemic hyperglycemia [7]. Insulin receptors are densely expressed in the hippocampus, entorhinal cortex, and prefrontal cortex regions that exhibit selective vulnerability in AD [8]. Post-mortem brain analyses have demonstrated that IRS-1 serine phosphorylation correlates with Braak neurofibrillary tangle stage and the severity of cognitive decline [7]. Downstream consequences of impaired central insulin signaling include glycogen synthase kinase-3β (GSK-3β) disinhibition, tau hyperphosphorylation, reduced Aβ clearance, and suppressed neuronal survival signaling mechanistically connecting brain insulin resistance to both hallmarks of AD pathology [9].

1.4 Rationale for Exploring Antidiabetic Drugs in Alzheimer's Disease

Drug repurposing offers a pragmatic route to AD therapeutics. Antidiabetic agents have well-characterized safety profiles and established pharmacokinetics and act on molecular targets: insulin signaling restoration, neuroinflammation, mitochondrial function, and oxidative stress directly relevant to AD pathogenesis. Several converging lines of evidence support systematic evaluation of this strategy. Epidemiological analyses from large healthcare databases have identified reduced dementia incidence in patients treated with metformin and GLP-1 receptor agonists relative to other antidiabetic drug classes [10, 11]. Preclinical studies across multiple AD models consistently demonstrate cognitive preservation, amyloid clearance, and anti-inflammatory effects following antidiabetic drug administration [12, 13]. Early-phase clinical trials with intranasal insulin and liraglutide have produced biomarker and cognitive signals warranting larger follow-up studies [14, 15]. This systematic review evaluates the totality of this evidence with critical scientific rigor.

2. Shared Pathophysiological Mechanisms Between T2DM and Alzheimer's Disease

2.1 Insulin Resistance and Impaired Brain Glucose Metabolism

Cerebral glucose hypometabolism is detectable years before clinical AD symptoms emerge, making it one of the earliest biomarkers of disease progression [16]. FDG-PET studies consistently identify reduced glucose uptake in the posterior cingulate, parietal, and temporal cortices of individuals with mild cognitive impairment (MCI) and early AD, a pattern that mirrors the distribution of eventual neurodegeneration [17]. Brain insulin resistance in AD disrupts glucose utilization at multiple levels. Impaired insulin receptor tyrosine kinase activity reduces trafficking of glucose transporters GLUT3 and GLUT4 to the plasma membrane, limiting glucose import into neurons and astrocytes [18]. Downstream attenuation of PI3K/Akt signaling reduces hexokinase activity and glycolytic flux, further compromising neuronal energy production. The resulting energy deficit impairs synaptic transmission, long-term potentiation, and axonal transport processes critical to memory consolidation and neuronal integrity. Akt inactivation releases GSK-3β from tonic inhibitory phosphorylation at Ser9, allowing GSK-3β to phosphorylate tau at multiple pathological epitopes and to suppress glycogen synthase, further reducing glucose utilization [19]. Reduced Akt activity simultaneously impairs FOXO transcription factor phosphorylation, diminishing antioxidant gene expression and increasing cellular vulnerability to oxidative injury. The convergence of energy failure, tau pathology, and oxidative susceptibility at the level of impaired Akt signaling illustrates why central

insulin resistance occupies a mechanistically central position in AD pathogenesis.

2.2 Chronic Neuroinflammation and Microglial Activation

Neuroinflammation is a defining feature of AD, not merely a secondary response. Genome-wide association studies have repeatedly implicated microglial genes TREM2, CR1, and CD33 in AD risk, establishing a causal rather than correlative role for innate immune dysfunction [20]. In T2DM, systemic low-grade inflammation characterized by elevated TNF-α, IL-1β, and IL-6 promotes a neuroinflammatory microenvironment that synergizes with AD-intrinsic immune pathology. Proinflammatory cytokines generated peripherally cross a compromised blood-brain barrier (BBB) and activate central NF-κB signaling in microglia and astrocytes [21]. NF-κB-driven cytokine production amplifies BACE1 expression, the rate-limiting enzyme in amyloidogenic APP processing, accelerating Aβ production in an inflammation-dependent manner [22]. TNF-α activates c-Jun N-terminal kinase (JNK), which serine-phosphorylates IRS-1, creating a feed-forward loop in which neuroinflammation perpetuates central insulin resistance [9]. Microglial function becomes progressively impaired in this inflammatory milieu. Disease-associated microglia (DAM) phenotypes arise, characterized by enhanced cytokine secretion but reduced Aβ phagocytic capacity, the opposite of what would be therapeutically beneficial [23]. Reactive astrogliosis compounds neuronal injury by impairing glutamate recycling, disrupting ionic homeostasis, and reducing lactate provision to energy-depleted neurons. Targeting this neuroinflammatory component is therefore a legitimate objective for any candidate AD therapeutic.

2.3 Oxidative Stress and Mitochondrial Dysfunction

Neurons are metabolically among the most demanding cells in the body. Their reliance on sustained oxidative phosphorylation renders them acutely vulnerable to mitochondrial dysfunction and ROS accumulation. In both AD and T2DM, mitochondrial complex I and complex IV activities are measurably reduced in affected tissues, impairing ETC function and ATP synthesis while increasing electron leak and superoxide production [24]. Advanced glycation end-products (AGEs), which accumulate in chronically hyperglycemic states, bind RAGE receptors on neurons and microglia, triggering NF-κB activation and a further oxidative-inflammatory cascade [25]. Mitochondrial ROS directly modify APP processing: oxidative modifications to α-secretase and γ-secretase shift processing toward amyloidogenic pathways, increasing Aβ42 production [26]. Simultaneously, ROS-mediated inhibition of protein phosphatase 2A (PP2A), the major tau phosphatase, enhances tau phosphorylation through reduced dephosphorylation rather than increased kinase activity alone [27]. This interconnected relationship between mitochondrial dysfunction, oxidative stress, Aβ accumulation, and tau pathology forms a self-amplifying cycle. Interventions that interrupt any node of this cycle, whether through antioxidant mechanisms, mitochondrial support, or direct amyloid clearance, have the potential to attenuate the broader neurodegenerative cascade.

2.4 Amyloid-β Accumulation and Tau Hyperphosphorylation

Aβ peptides arise from sequential cleavage of amyloid precursor protein (APP) by BACE1 and γ-secretase. Under physiologically normal conditions, Aβ is cleared through multiple mechanisms: enzymatic degradation by IDE and neprilysin, receptor-mediated transcytosis across the BBB via LRP1, and glymphatic drainage during sleep [28]. Each of these clearance routes is compromised in the context of T2DM-associated insulin resistance. IDE preferentially degrades insulin when circulating insulin concentrations are elevated, reducing Aβ catabolism. LRP1-mediated transcytosis is impaired by BBB dysfunction and reduced LRP1 expression in diabetic cerebrovascular disease [29]. Tau pathology in AD involves pathological hyperphosphorylation at more than 40 serine and threonine residues, leading to microtubule detachment and intraneuronal aggregation as neurofibrillary tangles (NFTs). GSK-3β and CDK-5 are the primary tau kinases implicated, both activated downstream of impaired insulin signaling [19]. More recently, mTORC1-mediated suppression of PP2A has been identified as an additional mechanism connecting insulin resistance to tau pathology, one that is particularly relevant to metformin's therapeutic potential via AMPK-mediated mTORC1 inhibition [30].

2.5 Vascular Dysfunction and Blood-Brain Barrier Impairment

Cerebrovascular integrity is essential for neuronal homeostasis. T2DM promotes progressive neurovascular pathology through endothelial dysfunction, pericyte loss, basement membrane thickening, and reduced tight junction protein expression [31]. These changes increase paracellular BBB permeability, allowing peripheral inflammatory mediators to enter the CNS, and simultaneously reduce the efficiency of active transport systems responsible for nutrient delivery and Aβ efflux. Pericyte loss, accelerated by hyperglycemia-induced oxidative stress, is mechanistically linked to Aβ accumulation: pericyte depletion reduces LRP1-mediated Aβ efflux and impairs cerebral blood flow autoregulation [32]. BBB dysfunction has an additional consequence often overlooked in therapeutic planning: it limits the predictability of CNS drug exposure for peripherally administered agents. Drugs that penetrate an intact BBB may achieve higher CNS concentrations in individuals with diabetes-related BBB disruption, complicating dose-response relationships in this population.

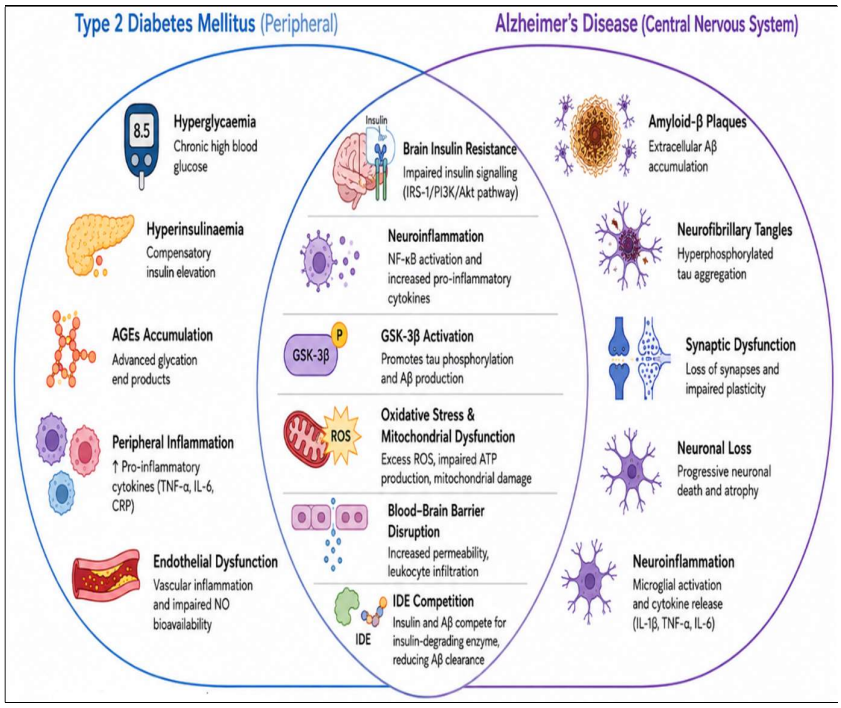


Figure 1 Overlapping Mechanistic Pathways Between T2DM and AD

3. Overview of Antidiabetic Drugs

3.1 Metformin

Metformin is the globally recommended first-line pharmacological agent for T2DM. It is a hydrophilic biguanide that acts primarily by inhibiting mitochondrial complex I in hepatocytes, raising the cellular AMP/ATP ratio and activating AMP-activated protein kinase (AMPK) [33]. AMPK activation reduces hepatic gluconeogenesis, improves peripheral insulin sensitivity, inhibits mTORC1, and activates autophagy. Metformin's pleiotropic anti-inflammatory and senolytic properties have drawn interest beyond metabolic disease. CNS penetration relies on organic cation transporters (OCT1, OCT2, MATE1), which have limited BBB expression, resulting in measurable but substantially sub-plasma CSF concentrations [34].

3.2 GLP-1 Receptor Agonists

GLP-1 receptor agonists (GLP-1 RAs) mimic endogenous glucagon-like peptide-1, stimulating glucose-dependent insulin secretion, suppressing glucagon, delaying gastric emptying, and promoting satiety. Approved agents include liraglutide, semaglutide, exenatide, dulaglutide, and tirzepatide (dual GIP/GLP-1). GLP-1 receptors are expressed throughout the brain, particularly in the hippocampus, hypothalamus, and brainstem, where activation mediates neurotrophic, anti-apoptotic, and anti-inflammatory signaling [35]. Several GLP-1 RAs cross the BBB via receptor-mediated transcytosis, though penetration efficiency varies considerably between agents.

3.3 DPP-4 Inhibitors

DPP-4 inhibitors (gliptins) prevent enzymatic degradation of endogenous GLP-1 and GIP, extending incretin bioavailability. Sitagliptin, vildagliptin, saxagliptin, and alogliptin are the principal agents. Beyond incretin enhancement, DPP-4 cleaves multiple neuropeptides, including neuropeptide Y (NPY), stromal cell-derived factor-1α (SDF-1α), and substance P substrates with roles in neuroinflammation, neurogenesis, and synaptic modulation [36]. DPP-4 inhibitors are orally bioavailable, well-tolerated, and carry low intrinsic hypoglycemia risk.

3.4 Thiazolidinediones

Thiazolidinediones (TZDs) are selective PPAR-γ (peroxisome proliferator-activated receptor-gamma) agonists that regulate adipogenesis, lipid metabolism, and inflammatory gene transcription. Pioglitazone and rosiglitazone are the established agents. PPAR-γ is expressed in neurons, microglia, and astrocytes, where its activation drives anti-inflammatory gene expression and promotes microglial polarization toward a phagocytic, anti-inflammatory phenotype [37]. Pioglitazone achieves superior CNS penetration relative to rosiglitazone and is the preferred agent in neurological research.

3.5 Insulin and Intranasal Insulin

Systemic insulin therapy encompasses multiple formulations targeting peripheral glucose homeostasis. In the CNS, insulin signaling through PI3K/Akt and MAPK/ERK cascades supports neuronal survival, synaptic plasticity, and memory consolidation [38]. Intranasal insulin (INI) delivery bypasses the BBB via olfactory and trigeminal nerve pathways, achieving direct brain parenchymal distribution without systemic metabolic effects. This route eliminates hypoglycemia risk and

enables pharmacological CNS insulin concentrations independent of peripheral metabolic status [39].

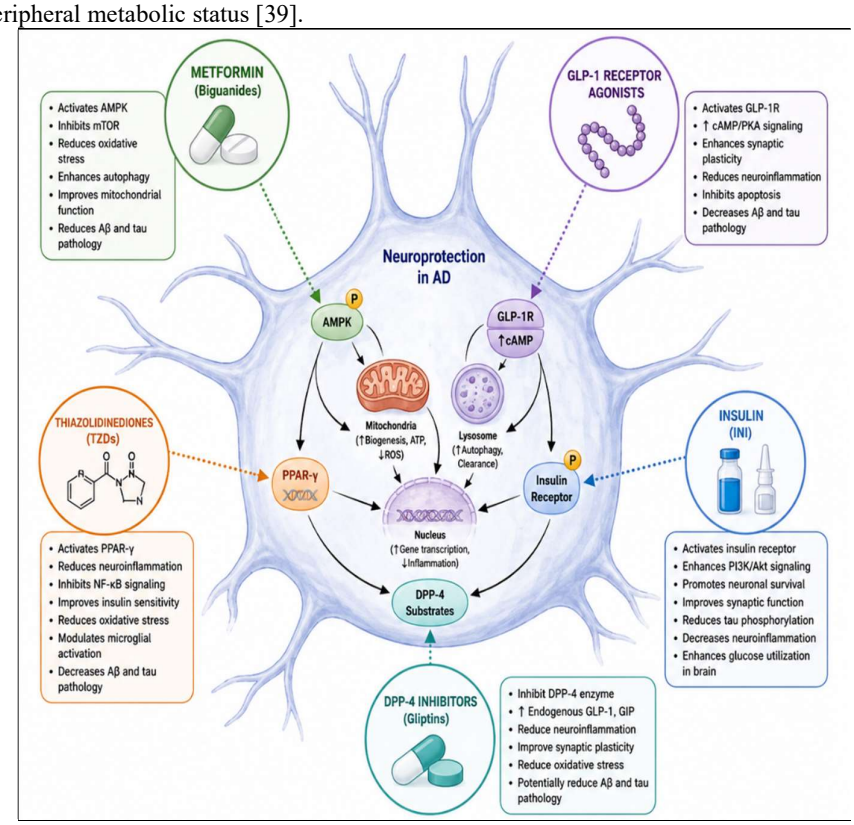


Figure 2 Neuroprotective Mechanisms of Antidiabetic Drug Classes

4. Neuroprotective Effects of Antidiabetic Drugs

4.1 Metformin: AMPK Activation, Neurogenesis, and Inflammation Control

Metformin's neuroprotective mechanisms converge on several interconnected pathways. AMPK activation inhibits mTORC1 kinase activity, restoring autophagic flux and improving clearance of intraneuronal Aβ oligomers and misfolded tau [40]. AMPK also phosphorylates TFEB (transcription factor EB), promoting lysosomal biogenesis and augmenting cellular protein quality control capacity, a mechanism relevant to both Aβ and tau clearance [41]. Pro-neurogenic effects of metformin have been demonstrated in murine hippocampal systems. Metformin activates an atypical protein kinase C–CREB-binding protein (PKC-CBP) pathway that stimulates adult hippocampal neurogenesis and enhances spatial memory acquisition [42]. BDNF expression is upregulated following metformin treatment, supporting synaptic plasticity in hippocampal circuits that are preferentially damaged in early AD. These neurogenic effects distinguish metformin from most other antidiabetic agents and suggest potential for structural neuroprotection rather than purely symptomatic benefit. In 5xFAD mice, a stringent model of accelerated amyloid pathology, metformin reduced amyloid plaque count, attenuated hippocampal neuroinflammatory markers (Iba-1, GFAP), and improved performance on spatial memory tasks [43]. Anti-inflammatory mechanisms involve NF-κB pathway suppression and inhibition of NLRP3 inflammasome assembly, reducing IL-1β maturation and secretion without impairing microglial phagocytic function [44]. Metformin also reduces circulating and CNS AGE levels, attenuating RAGE-driven oxidative and inflammatory signaling at the neurovascular unit [45]. Despite this mechanistic coherence, a critical limitation persists. Metformin is a polar cation requiring active transporter-mediated uptake to cross the BBB. OCT1 and MATE1 expression at the BBB is low compared with peripheral tissues, resulting in CSF concentrations substantially below plasma levels [34]. Whether these CSF concentrations are sufficient for pharmacodynamically meaningful AMPK activation in the human brain remains unresolved. This question is central to interpreting clinical data and designing future trials with appropriate PK/PD endpoints.

4.2 GLP-1 Receptor Agonists: Synaptic Protection and Reduced Amyloid Burden

GLP-1 receptor agonists have accumulated the most extensive neuroprotective evidence of any antidiabetic drug class. GLP-1 receptor activation in neurons stimulates cAMP production and PKA activation, phosphorylating CREB and increasing BDNF transcription [46]. The PI3K/Akt pathway co-activation promotes neuronal survival, inhibits GSK-3β, reduces tau phosphorylation, and supports dendritic spine maintenance, mechanistically addressing multiple AD-relevant targets simultaneously. Liraglutide has been studied most extensively in AD

models. In APP/PS1 transgenic mice, chronic liraglutide administration reduced total Aβ plaque count by approximately 30–40%, lowered soluble Aβ42 tissue concentrations, reduced BACE1 expression, and simultaneously increased IDE activity acting on both Aβ production and clearance [47]. Tau phosphorylation was attenuated at multiple epitopes, correlating with reduced GSK-3β activity and restored PP2A function. Behavioral outcomes consistently showed improved performance in spatial navigation and novel object recognition tasks. Semaglutide, with its enhanced GLP-1 receptor binding affinity and longer half-life, has demonstrated superior CNS penetration relative to liraglutide in pharmacokinetic studies [48]. In 3xTg-AD mice, semaglutide reduced amyloid plaque number, reversed hippocampal synaptic deficits, and lowered IL-6, IL-1β, and TNF-α expression in hippocampal tissue [49]. Notably, cognitive improvement persisted for several weeks after drug cessation in one study, suggesting disease-modifying rather than purely symptomatic activity, though this finding requires replication and mechanistic confirmation. Mitochondrial protection by GLP-1 RAs has been consistently reported. GLP-1 receptor activation reduces ROS generation, restores mitochondrial membrane potential, and increases PGC-1α expression, the master regulator of mitochondrial biogenesis [50]. These effects complement anti-amyloid and anti-tau actions, providing mechanistically comprehensive neuroprotection across multiple AD pathological domains. It must be noted, however, that most preclinical liraglutide and semaglutide studies used doses substantially higher than standard clinical antidiabetic doses, expressed as weight-adjusted equivalents. The extent to which human-equivalent therapeutic doses achieve comparable brain receptor occupancy and downstream signaling remains uncertain and is a legitimate challenge for clinical translation.

4.3 DPP-4 Inhibitors: Anti-inflammatory and Antioxidant Effects

DPP-4 inhibitors exert neuroprotection through both incretin-dependent and incretin-independent mechanisms. Elevating endogenous GLP-1 and GIP levels partially reproduces GLP-1 RA-mediated neuroprotective signaling, albeit at lower receptor occupancy due to competition with endogenous peptide degradation kinetics [51]. The direct neuroprotective effects of DPP-4 substrate preservation, particularly NPY and SDF-1α, may contribute additional CNS protection independent of incretin effects. Sitagliptin reduced Aβ42 plaque burden and attenuated tau phosphorylation at Thr231 in streptozotocin-induced AD rats, alongside reductions in hippocampal TNF-α and IL-1β levels [52]. Choline acetyltransferase (ChAT) activity, a marker of cholinergic neuron integrity, was preserved, suggesting protection of the cholinergic system that is critically depleted in AD. Vildagliptin demonstrated antioxidant neuroprotection through increased hippocampal SOD, catalase, and glutathione concentrations, with concurrent improvements in Morris water maze performance [53]. The clinical limitations of DPP-4 inhibitors in AD must be acknowledged. No adequately powered randomized trial has evaluated gliptins as primary AD therapeutics in non-diabetic populations. Available observational data suggest modest, inconsistent associations between DPP-4 inhibitor use and dementia risk in T2DM cohorts [54]. The mechanistic rationale is credible, but clinical translation remains at an early-stage relative to GLP-1 RAs and intranasal insulin.

4.4 Thiazolidinediones: PPAR-γ Mediated Neuroprotection

PPAR-γ agonism by TZDs drives anti-inflammatory and anti-amyloidogenic transcriptional programs in multiple CNS cell types. In microglia, PPAR-γ activation suppresses NF-κB nuclear translocation, reducing TNF-α, IL-6, and IL-12p40 production while simultaneously enhancing Aβ phagocytosis and clearance efficiency [55]. This dual mechanism suppressing inflammation while improving Aβ removal represents a mechanistically attractive combination for AD therapeutics. Pioglitazone reduced Aβ plaque burden, improved spatial memory, and attenuated astrogliosis in APP/PS1 mice [56]. It reduced tau phosphorylation via GSK-3β inhibition downstream of Akt activation and improved BBB integrity by restoring pericyte coverage and tight junction protein expression (occludin and claudin-5) in diabetic animal models [57]. Mitochondrial effects of pioglitazone include direct targeting of mitochondrial PPAR-γ, reducing ETC complex dysfunction and mitochondrial ROS production through mechanisms partially independent of nuclear transcription [58]. The clinical picture for TZDs in AD is distinctly mixed. An early trial of rosiglitazone in mild-to-moderate AD patients demonstrated cognitive benefit in APOE4-negative participants, but a larger subsequent trial failed to confirm this finding in an unselected population [59]. Pioglitazone was evaluated in the TOMORROW prevention trial at 0.8 mg/day in cognitively normal high-risk individuals; the trial was terminated early due to futility [60]. The dose selected to minimize bladder cancer risk likely achieved insufficient CNS PPAR-γ receptor occupancy, a pharmacological limitation that confounds interpretation of the null result. The bladder cancer signal associated with high-dose long-term pioglitazone further limits applicability in older populations [61].

4.5 Insulin Therapy and Intranasal Insulin

Systemic insulin therapy in T2DM, when maintained at near-normoglycemic targets from early in the disease course, is associated with reduced long-term dementia risk in population-based analyses. The ACCORD-MIND substudy demonstrated that intensive glycemic control preserved hippocampal volume relative to standard care; however, no significant cognitive benefit was identified at the primary analysis, and recurrent hypoglycemia in the intensive arm may have attenuated any neuroprotective effect [62]. Intranasal insulin has generated the most clinically compelling human data in the antidiabetic-AD field. Following intranasal administration, insulin distributes to the olfactory bulb, hippocampus, and hypothalamus within minutes via perineural and perivascular pathways, bypassing the BBB entirely [63].

This achieves pharmacologically relevant brain insulin concentrations without peripheral metabolic consequences. The SNIFF phase 2 trial enrolled 240 adults with MCI or mild AD and administered INI at 20 IU or 40 IU twice daily versus placebo over 12 months [64]. The 20 IU arm achieved a statistically significant improvement in the primary cognitive endpoint (ADAS-Cog-12) compared to placebo in the overall population. CSF biomarker analyses showed trends toward reduced phospho-tau and improved Aβ42/40 ratios. APOE4-negative participants showed more pronounced benefits, a pharmacogenomic pattern that has now been observed across multiple antidiabetic AD trials and has important implications for patient stratification. Mechanistically, INI restores hippocampal BDNF expression, reduces GSK-3β activity, improves synaptic vesicle protein density, and normalizes glucose transporter expression at synaptic terminals [65]. Hypothalamic effects include modulation of the HPA axis, reducing cortisol-mediated hippocampal injury. Delivery device design, insulin formulation, nasal mucosal health, and technique consistency are practical variables that influence CNS drug distribution and require standardization across future trials.

Table 1. Some Antidiabetic Drug Classes, Mechanisms of Action, and Neuroprotective Evidence in Alzheimer's Disease

Drug Class & Commonly Studied Agents	Primary Mechanism	Neuroprotective Pathways	BBB Penetration	Evidence Level	References
Biguanides, Metformin	AMPK activation; mitochondrial complex I inhibition	↓ mTORC1/↑ autophagy; ↓ NF-κB; ↑ neurogenesis (PKC-CBP); ↓ NLRP3; ↓ AGE/RAGE; ↓ tau-P via PP2A	Limited (OCT1/OCT2-dependent; low BBB transporter expression)	Preclinical: strong. Clinical: emerging	[33, 34, 40, 41, 42, 43, 44, 45]
GLP-1 Receptor Agonists, Liraglutide, Semaglutide, Exenatide	GLP-1R agonism → cAMP/PKA; PI3K/Akt activation	↓ Aβ (↓BACE1, ↑IDE); ↓ tau-P (↓GSK-3β, ↑PP2A); ↑ BDNF; ↑ PGC-1α/mitochondrial biogenesis; ↓ neuroinflammation	Moderate (receptor-mediated transcytosis; semaglutide > liraglutide)	Preclinical: very strong. Clinical: promising	[35, 46, 47, 48, 49, 50]
DPP-4 Inhibitors, Sitagliptin, Vildagliptin, Alogliptin	DPP-4 inhibition → ↑ GLP-1/GIP; preservation of NPY, SDF-1α	↓ NF-κB; ↓ oxidative stress; ↑ ChAT; ↓ Aβ42; ↓ tau-P (Thr231); ↑ hippocampal antioxidants	Moderate	Preclinical: strong. Clinical: limited	[36, 51, 52, 53, 54]
Thiazolidinediones, Pioglitazone, Rosiglitazone	PPAR-γ nuclear agonism	↓ NF-κB neuroinflammation; ↑ Aβ phagocytosis; ↓ GSK-3β; ↑ eNOS; ↑ tight junction proteins; mitochondrial ROS reduction	Pioglitazone: good. Rosiglitazone: poor	Preclinical: strong. Clinical: mixed/negative	[37, 55, 56, 57, 58, 59, 60]
Insulin (Intranasal)	Regular insulin, Insulin detemir	Insulin receptor → PI3K/Akt; MAPK/ERK	↑ BDNF; ↓ GSK-3β; ↑ synaptic density; ↑ GLUT3/GLUT4; HPA axis modulation	Direct CNS via olfactory/trigeminal pathways (bypasses BBB)	Clinical: most promising (Phase 2 positive)

5. Evidence from Preclinical and Clinical Studies

5.1 Animal Models of Alzheimer's Disease

Transgenic and chemically induced animal models have underpinned the preclinical neuroprotective case for antidiabetic drugs. The most frequently employed models include APP/PS1, 5xFAD, 3xTg-AD, and APPswe/PSEN1dE9 transgenic lines, alongside streptozotocin-induced central insulin resistance (ICV-STZ) models that specifically recapitulate the metabolic dimension of AD-like pathology [66]. In APP/PS1 mice, metformin administration over 12 weeks produced approximately 30–40% reduction in hippocampal amyloid plaque load, attenuated Iba-1-positive microglial activation, and improved spatial memory in the Morris water maze and novel object recognition tests [43]. Liraglutide produced comparable amyloid reductions with additional improvements in dendritic spine density and synaptic vesicle marker expression [47]. Pioglitazone reduced plaque count, attenuated astrogliosis, and preserved working memory in radial-arm maze testing [56]. ICV-STZ models have been particularly informative for evaluating antidiabetic drugs targeting brain insulin resistance directly. In these animals, sitagliptin restored hippocampal insulin receptor expression, normalized GSK-3β activity, and reduced tau phosphorylation, improving spatial learning in the water maze [67]. Metformin in ICV-STZ rats additionally restored hippocampal acetylcholinesterase activity and reduced lipid peroxidation markers, reinforcing its multi-target neuroprotective scope. The limitations of these models are significant and must temper interpretation. Transgenic AD models overexpress familial AD mutations representing fewer than 5% of human AD cases. Sporadic AD, which accounts for the overwhelming majority of clinical cases, involves complex gene-environment interactions, microbiome contributions, and age-dependent metabolic changes that are poorly represented in standard transgenic lines [68]. Furthermore, the typical practice of initiating treatment before pathology onset in animal studies does not reflect the clinical scenario, where intervention occurs after established MCI or AD diagnosis. This temporal mismatch is a primary contributor to the preclinical-clinical translation gap observed across AD drug development broadly.

5.2 Observational Studies in Diabetic Patients

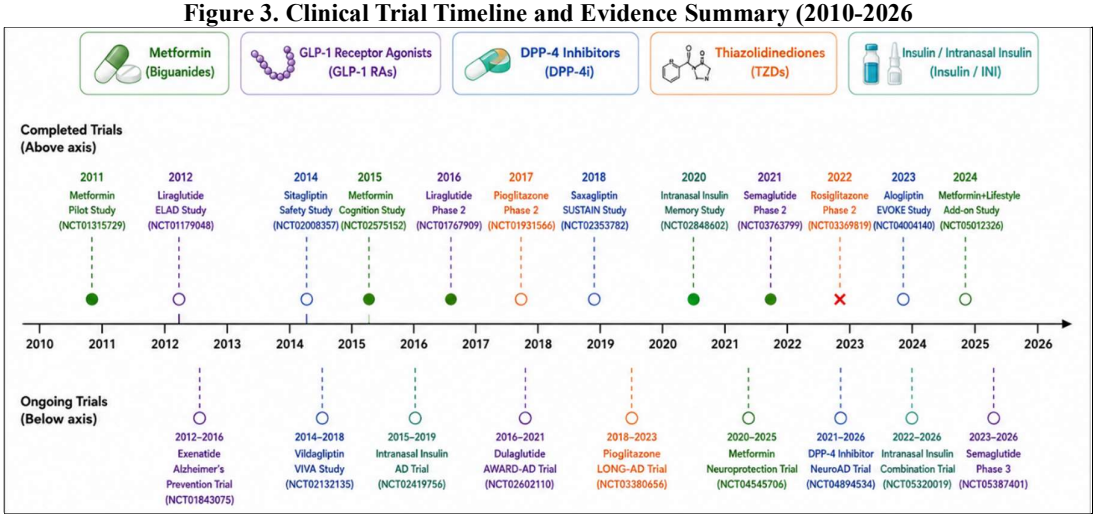
Population-level observational data provide valuable epidemiological context. A large retrospective analysis of the Taiwan National Health Insurance Database found that metformin use was associated with significantly lower incidence of dementia compared with other antidiabetic

agents (adjusted hazard ratio 0.76; 95% CI: 0.71–0.81) after adjustment for multiple confounders [69]. A UK population-based cohort study found reduced AD incidence in patients prescribed GLP-1 RAs versus DPP-4 inhibitors and sulfonylureas, with the association persisting after adjustment for HbA1c, BMI, and cardiovascular comorbidities [70]. A nested case-control study using the UK Clinical Practice Research Datalink (CPRD) found pioglitazone use associated with approximately 23% reduced dementia risk, with evidence of dose and duration dependence [71]. These observational findings are hypothesis-generating and mechanistically plausible, but causation cannot be inferred. Confounding by indication remains a substantial threat to these analyses. Patients selected for newer drug classes such as GLP-1 RAs typically have fewer comorbidities and more active clinical management, both associated independently with lower dementia risk. Reverse causation is also plausible: early cognitive impairment may prompt medication discontinuation, artificially inflating dementia rates among non-users. These biases cannot be fully addressed in observational frameworks and underscore the necessity of randomized trial evidence.

5.3 Clinical Trials Completed and Ongoing

The SNIFF (Study of Nasal Insulin to Fight Forgetting) trial was a phase 2, randomized, placebo-controlled trial enrolling 240 adults with MCI or mild AD [64]. Participants received INI at 20 IU or 40 IU twice daily for 12 months. The 20 IU arm achieved statistically significant improvement on the ADAS-Cog-12 relative to placebo. CSF biomarker trends suggested reduced phospho-tau and improved Aβ42/40 ratios. The effect was more pronounced in APOE4-negative participants, establishing a pharmacogenomic pattern warranting further investigation. The 40 IU arm did not show consistent benefit, suggesting a non-linear dose-response relationship that requires mechanistic explanation. The LINA trial (Liraglutide in Alzheimer's Disease) was a phase 2b UK randomized trial evaluating daily subcutaneous liraglutide 1.8 mg against placebo in 204 patients with mild AD over 12 months [15]. FDG-PET cerebral glucose metabolism served as the primary outcome. The liraglutide arm demonstrated significantly attenuated decline in posterior cortical FDG-PET uptake, a robust biomarker of AD-related metabolic deterioration, compared to placebo. Secondary cognitive endpoints showed a trend toward preservation but did not reach statistical significance, likely reflecting the trial's limited power and duration. The TOMORROW trial evaluated pioglitazone 0.8 mg/day in cognitively normal adults at high genetic risk of MCI onset within 5 years. The trial was terminated early for futility; pioglitazone at this dose did not delay MCI onset [60]. The null result is difficult to interpret definitively. The dose was selected to minimize bladder cancer risk and may have been insufficient for meaningful CNS PPAR-γ occupancy. Participants were enriched on genetic risk alone, without biomarker confirmation of preclinical amyloid pathology, meaning the treated population was heterogeneous in terms of actual AD pathological burden. The ACCORD-MIND substudy found that intensive glycemic control preserved hippocampal volume on MRI but did not produce a statistically significant cognitive benefit over standard care in T2DM patients [62]. Recurrent hypoglycemia in the intensive arm is a known independent risk factor for cognitive injury, likely attenuating any neuroprotective benefit, creating an internal confound within the trial design.

Figure 3. Clinical Trial Timeline and Evidence Summary (2010-2026



5.4 Strengths and Limitations of Current Evidence

The mechanistic coherence and reproducibility of preclinical findings constitute genuine scientific strengths. Multiple independent groups, using distinct AD models and drug classes, have converged on consistent findings: antidiabetic drugs reduce Aβ burden, attenuate tau pathology, suppress neuroinflammation, and improve cognitive performance. This cross-drug, cross-model consistency strengthens the mechanistic hypothesis. Clinical evidence, however, is substantially weaker. Most

completed trials were underpowered, enrolled heterogeneous populations without amyloid biomarker stratification, used outcome measures poorly sensitive to early disease-modifying effects, and were of insufficient duration to detect neuroprotective signals in a slowly progressive condition. The field has progressed significantly in trial methodology. Amyloid PET and blood-based biomarkers (plasma p-tau217, NfL) are now viable enrollment tools, and future trials should leverage these advances.

Table 2. Selected Ongoing and Recently Initiated Clinical Trials of Antidiabetic Drugs in Alzheimer's Disease

Trial Name	Drug	Phase	Target Population	Primary Endpoint	Estimated Completion	ClinicalTrials.gov ID	References
EVOKE / EVOKE+	Semaglutide 2.4 mg SC weekly	Phase 3	Early AD-biomarker-confirmed MCI/Mild AD	CDR-SB; amyloid PET change	2025–2026	NCT04777396	[48, 49, 50]
SNIFF Phase 3 Extension	Intranasal Insulin 20 IU BID	Phase 3	MCI/Mild AD	ADAS-Cog; CSF p-tau; Aβ42/40	2025	NCT01767909	[63, 64, 65]
TAME-AD (Metformin in MCI)	Metformin 2000 mg/day oral	Phase 2	MCI — non-diabetic older adults	Cognitive composite; plasma NfL; Aβ42/40	2026	NCT04098666	[40, 41, 43, 75]
Ex-FEEDER	Exenatide SC	Phase 2	Mild-Moderate AD	FDG-PET; MRI volumetrics; cognitive composites	Ongoing	NCT01255163	[35, 46]
GLP-1 RA + Omega-3 Combination	Liraglutide + Omega-3 FA	Phase 2	T2DM with comorbid MCI	FDG-PET CMRgl; ADAS-Cog	2025	NCT04120610	[15, 47]

6. Challenges and Limitations

6.1 Conflicting Clinical Outcomes

The most consistent challenge in this field is the discordance between mechanistically compelling preclinical evidence and modest or null clinical outcomes. This gap is well recognized in AD drug development broadly but is particularly instructive for antidiabetic drug repurposing, given the strength of preclinical data. Several factors plausibly explain this discordance. First, preclinical models predominantly treat young animals prior to pathological onset. In clinical practice, patients present after years of established neurodegeneration, with significant synaptic loss and neuronal dropout that cannot be recovered. Second, mouse models do not replicate the genetic, epigenetic, and environmental complexity of sporadic human AD. Third, most completed clinical trials enrolled participants without biomarker confirmation of amyloid pathology, meaning a significant proportion may not have had true AD, diluting any real drug effect toward null in intention-to-treat analyses.

6.2 Dose and Duration Issues

Optimal dosing for neuroprotection has not been established for any antidiabetic agent in the AD context. Standard antidiabetic doses are calibrated for peripheral metabolic endpoints and may achieve insufficient CNS concentrations for pharmacodynamic target engagement. The TOMORROW trial at pioglitazone 0.8 mg/day selected to minimize bladder cancer risk almost certainly illustrates this problem. At the other end of the spectrum, the SNIFF trial's 40 IU INI arm produced no cognitive benefit despite the higher dose, suggesting that dose-response relationships in the CNS may be non-linear or bell-shaped, as has been observed with insulin signaling in hippocampal preparations [72]. Treatment duration is equally important. Neurodegeneration in AD evolves over decades. Most completed trials spanned 12–24 months, which is likely insufficient to detect disease-modifying effects on cognitive trajectories. Surrogate endpoints amyloid PET quantification, CSF phospho-tau, and plasma NfL are more sensitive to early biological effects and should be co-primary outcomes in future trials rather than tertiary analyses.

6.3 Blood-Brain Barrier Penetration

BBB penetration is a pharmacokinetic determinant of CNS drug efficacy that deserves more systematic attention in antidiabetic drug trials. Metformin's transporter-dependent penetration is limited and variable between individuals based on OCT1 polymorphisms [34]. Rosiglitazone has minimal CNS penetration in humans, which may entirely explain its clinical inefficacy in AD trials [59]. For GLP-1 RAs, penetration efficiency differs between agents: semaglutide's higher albumin binding may facilitate neonatal Fc receptor (FcRn)-mediated transcytosis more effectively than liraglutide [48]. CNS penetration in diseased brains with T2DM-related BBB dysfunction may differ from what is observed in healthy preclinical models or healthy human volunteers. Paradoxically, a more permeable BBB in diabetic individuals might enhance passive drug penetration while simultaneously impairing active efflux transporter function, with net effects on drug CNS exposure that are difficult to predict without direct measurement. Future trials should routinely incorporate PK/PD modeling and, where feasible, CSF drug concentration measurement.

6.4 Risk of Hypoglycaemia in Non-Diabetic Populations
Repurposing glucose-lowering drugs in non-diabetic AD patients introduces hypoglycemia as a safety concern. Hypoglycemia causes acute cognitive impairment and, with recurrent episodes, accelerates hippocampal atrophy and independently increases dementia risk [73]. Agents with intrinsically low hypoglycemia risk, metformin, DPP-4 inhibitors, and GLP-1 RAs are pharmacologically preferable for non-diabetic trial participants. Their glucose-lowering mechanisms are glucose-dependent or hepatically targeted, substantially reducing hypoglycemia probability. INI delivery eliminates systemic insulin exposure, but nasal device failure or technique variability could result in inadvertent systemic absorption, warranting protocol-level monitoring in clinical trials.

7. FUTURE PERSPECTIVES

7.1 Drug Repurposing Strategies
Antidiabetic drugs are well-positioned for systematic repurposing in AD. Network pharmacology approaches mapping drug targets onto AD molecular interaction networks have identified metformin and GLP-1 RAs as agents with high connectivity to AD-relevant disease modules [74]. Computational drug-disease matching platforms, including those integrating transcriptomic disease signatures with drug perturbation databases, have repeatedly flagged antidiabetic drugs as high-confidence repurposing candidates. These computational prioritization strategies should guide the selection and sequencing of clinical trials. The TAME (Targeting Ageing with Metformin) trial, a landmark multicenter study evaluating metformin in age-related condition prevention, will generate foundational data on metformin's effects on aging biomarkers, cognitive trajectories, and comorbidity burden in a non-diabetic population [75]. Its outcomes will significantly inform the design of metformin trials in preclinical AD.

7.2 Combination Therapy Antidiabetic Drugs and Disease-Modifying Agents
The regulatory approvals of lecanemab and donanemab as anti-amyloid immunotherapies mark a shift in the AD treatment landscape. These agents reduce amyloid plaque burden but do not directly address tau pathology, neuroinflammation, or metabolic dysfunction pathological domains where antidiabetic drugs are active. Combination strategies pairing anti-amyloid immunotherapy with a metabolic neuroprotective agent are mechanistically logical and may produce additive or synergistic benefits [76]. Tau-targeting agents under development could similarly benefit from co-administration with antidiabetic drugs that reduce upstream tau kinase activity. As the AD treatment landscape becomes increasingly combination-oriented, antidiabetic drugs, given their safety profiles, generic availability, and multi-target mechanisms, are natural candidates for add-on trial evaluation.

7.3 Precision Medicine and Pharmacogenomics
The consistent pattern of APOE4-negative patients responding more favorably to antidiabetic interventions observed in trials of rosiglitazone, intranasal insulin, and INI detemir strongly suggests that APOE genotype influences pharmacological response [59, 64, 77]. APOE4 may impair GLP-1 receptor-mediated lipid signaling, alter insulin receptor trafficking, or modify inflammatory responses in ways that attenuate drug efficacy. Prospective pharmacogenomic stratification by APOE status should be mandatory in future antidiabetic AD trials. Beyond APOE4, polymorphisms in OCT1 (affecting metformin uptake), GLP1R (affecting receptor sensitivity), and PPARG (affecting TZD efficacy) are candidate pharmacogenomic variables. Incorporating these into trial stratification will enable identification of responding subpopulations, rescue trials that might otherwise show null results in unselected populations and guide personalized prescribing if regulatory approval is eventually sought.

7.4 BBB-Targeted and Nanoparticle Drug Delivery
Enhancing CNS delivery of antidiabetic drugs is a tractable research priority. Nasal lipid nanoparticle formulations of metformin have been evaluated in preclinical models, demonstrating significantly improved hippocampal drug concentrations compared to oral administration with associated improvements in cognitive and inflammatory endpoints [78]. Solid lipid nanoparticles and polymeric nanoparticles functionalized with transferrin receptor ligands or apolipoprotein E peptides can exploit receptor-mediated BBB transcytosis to deliver otherwise poorly penetrant drugs to the brain parenchyma. For GLP-1 RAs, structural modification strategies, including CNS-optimized analogs with enhanced FcRn-mediated transcytosis, are under development. These approaches may enable CNS-targeted GLP-1 receptor agonism at doses below those producing systemic metabolic effects, a pharmacologically useful separation that could expand the applicable patient population.

7.5 Early Intervention in Prediabetes and Preclinical AD
The window of maximum therapeutic opportunity for both AD and T2DM is the preclinical phase before significant neuronal loss or overt cognitive decline. Individuals with prediabetes, insulin resistance, or metabolic syndrome who also carry early AD biomarker signals (elevated plasma p-tau217, reduced Aβ42/40 ratio) represent a biologically defined high-risk population for early antidiabetic drug intervention. Blood-based AD biomarkers have reached sufficient analytical performance for population-scale screening, making biomarker-enriched prevention trials increasingly feasible [79]. Lifestyle interventions reducing insulin resistance, structured aerobic exercise, the Mediterranean diet, and weight loss consistently attenuate AD biomarker trajectories in epidemiological and intervention studies. Pharmacological augmentation with metformin or a GLP-1 RA in high-risk prediabetic individuals with confirmed preclinical amyloid pathology represents a scientifically grounded and practically feasible prevention trial design that warrants priority investment.

8. Advantages and Limitations of Antidiabetic Drug Classes in AD Therapeutics

8.1 Metformin

Metformin holds several practical advantages as a candidate neuroprotective agent. It is generic, widely available, and among the least expensive antidiabetic drugs globally, a consideration that is relevant significantly for long-term trial feasibility and eventual clinical accessibility. Its safety profile spans several decades of real-world use across diverse populations, including older adults with multiple comorbidities. At the mechanistic level, metformin's AMPK-mediated neuroprotection is genuinely multi-target: it simultaneously suppresses mTORC1 to restore autophagic flux, inhibits NF-κB-driven neuroinflammation, promotes adult hippocampal neurogenesis via the PKC-CBP pathway, inhibits NLRP3 inflammasome assembly, and attenuates AGE/RAGE-driven oxidative signaling at the neurovascular unit [44, 69]. Epidemiological support is substantial, with large database analyses consistently identifying lower dementia incidence in metformin-treated diabetic patients relative to other antidiabetic drug classes [69]. Despite these strengths, metformin faces a significant pharmacokinetic limitation in the CNS context. It is a hydrophilic cation that relies on organic cation transporters, primarily OCT1 and OCT2, for cellular uptake. Expression of these transporters at the blood-brain barrier is low, resulting in CSF concentrations that are measurably present but substantially below plasma levels [34]. Whether these concentrations are sufficient for pharmacodynamic AMPK activation in the human hippocampus remains unresolved. Renal dose restriction in older adults, a population at greatest AD risk, further limits maximum achievable dosing. No phase 3 clinical trial specifically targeting AD with metformin has been completed to date. Translational readiness is therefore classified as moderate: a phase 2 trial in non-diabetic adults with MCI is ongoing (TAME-AD, NCT04098666), and CNS-targeted delivery strategies including nasal nanoparticle formulations are under preclinical evaluation [34, 44, 69, 75].

8.2 GLP-1 Receptor Agonists

GLP-1 receptor agonists carry the strongest preclinical neuroprotective evidence of any antidiabetic drug class. Their mechanistic profile is comprehensive, simultaneously reducing Aβ production (via BACE1 suppression), enhancing Aβ clearance (via IDE upregulation), attenuating tau phosphorylation (via GSK-3β inhibition and PP2A restoration), promoting mitochondrial biogenesis (via PGC-1α), and suppressing microglial neuroinflammation all through a single receptor-mediated signaling cascade [48, 49, 50]. Clinically, liraglutide has produced biomarker-confirmed signals of CNS activity: the LINA trial demonstrated significantly attenuated posterior cortical FDG-PET metabolic decline over 12 months in mild AD patients [15]. A consistent pharmacogenomic pattern has emerged across studies, with APOE4-negative participants showing more pronounced cognitive and biomarker benefits, a finding that has important implications for trial stratification and patient selection [15, 48]. The key limitations are practical rather than mechanistic. Most approved GLP-1 RAs require subcutaneous injection, which introduces adherence challenges in cognitively impaired populations and limits acceptability in non-diabetic AD trial participants. Drug cost remains high, restricting both trial participation and eventual clinical access in low- and middle-income settings. CNS dose equivalency is uncertain: the doses used in preclinical AD studies, when converted to weight-adjusted human equivalents, often exceed standard approved clinical doses, raising questions about whether therapeutic exposures achieve comparable brain receptor occupancy [48]. Translational readiness is high in the phase 3 EVOKE and EVOKE+ Trials of semaglutide in biomarker-confirmed early AD are the field's most advanced ongoing evaluation of any antidiabetic drug in this indication [15, 48, 49, 50].

8.3 DPP-4 Inhibitors

DPP-4 inhibitors offer an attractive tolerability profile for AD repurposing. They are orally administered, carry minimal hypoglycemia risk, are weight-neutral, and are generally well-tolerated in elderly populations-characteristics that are particularly important when considering use in non-diabetic, cognitively impaired older adults. Their anti-inflammatory and antioxidant effects are pharmacologically meaningful: preservation of NPY, SDF-1α, and other DPP-4 substrates provides CNS-relevant neuropeptide signaling independent of incretin effects, and preclinical data show reductions in hippocampal oxidative markers and NF-κB-driven cytokine production [51, 52, 53]. The clinical limitation of this class is the relative weakness of receptor-level neuroprotection compared with direct GLP-1 receptor agonists. By elevating endogenous GLP-1 rather than pharmacologically saturating its receptor, DPP-4 inhibitors achieve modest incretin receptor occupancy that is unlikely to replicate the full neuroprotective signaling amplitude of GLP-1 RAs [51]. No phase 2 or phase 3 trial has evaluated any gliptin as a primary AD therapeutic in a non-diabetic population. Available clinical data come largely from observational analyses in T2DM cohorts with inconsistent and modest associations [54]. CNS penetration data in humans are limited. Translational readiness is therefore low-to-moderate: the preclinical mechanistic rationale is credible, and the safety profile is favorable, but clinical translation remains at an early stage and requires dedicated trial investment [51, 52, 53, 54].

8.4 Thiazolidinediones (Pioglitazone)

Pioglitazone's PPAR-γ-mediated neuroprotective mechanisms are mechanistically compelling. In microglia, PPAR-γ activation drives anti-inflammatory polarization and enhances Aβ phagocytic capacity simultaneously, an unusual combination that addresses both neuroinflammation and impaired protein clearance in a single transcriptional program [57]. Pioglitazone additionally improves BBB integrity through pericyte preservation and tight junction protein upregulation and provides mitochondrial protection through mechanisms

partially independent of nuclear PPAR-γ activation [57, 60]. Among the TZDs, pioglitazone achieves relatively good CNS penetration, making it the pharmacokinetically preferred agent for neurological research within this class. However, the clinical picture is sobering. The TOMMORROW phase 3 trial failed to demonstrate a delay in MCI onset with pioglitazone 0.8 mg/day in cognitively normal high-risk individuals [60]. The dose selected was constrained by the known bladder cancer risk associated with high-dose, long-term pioglitazone and almost certainly achieved insufficient CNS PPAR-γ receptor occupancy, creating an internal pharmacological confound that makes the null result difficult to interpret as true drug inefficacy. Bladder cancer risk with prolonged high-dose use, fluid retention, and cardiac complications further limit applicability in older populations who represent the primary AD therapeutic target [61]. The APOE4-negative pharmacogenomic pattern observed with rosiglitazone in earlier trials constrains generalisability to unselected AD populations. Translational readiness is low-to-moderate: future trials, if pursued, require biomarker-enriched populations, dose optimization with CNS exposure confirmation, and careful safety monitoring [57, 60, 61].

8.5 Intranasal Insulin

Intranasal insulin addresses the single most fundamental pharmacokinetic challenge in antidiabetic drug repurposing for AD BBB penetration by bypassing the barrier entirely. Olfactory and trigeminal nerve pathways deliver insulin directly to the brain parenchyma within minutes of intranasal administration, achieving pharmacologically relevant hippocampal and CSF concentrations without systemic metabolic exposure [63]. This eliminates hypoglycemia risk, which is a critical safety advantage when treating non-diabetic older adults. The SNIFF phase 2 trial produced a statistically significant positive primary cognitive endpoint in the 20 IU arm, alongside favorable CSF biomarker trends including reduced phospho-tau and improved Aβ42/40 ratios [64]. The APOE4-negative benefit pattern is consistent with findings across the broader antidiabetic AD field [64, 65]. The limitations are primarily practical and pharmacokinetic. Delivery device variability introduces inconsistency in nasal drug deposition and CNS distribution between patients and across study sites, a challenge that requires device standardization as a protocol-level priority in future trials [63]. The dose-response relationship is demonstrably non-linear: the 40 IU arm of the SNIFF trial produced no consistent cognitive benefit despite delivering twice the drug dose, suggesting possible bell-shaped receptor-level response kinetics that require mechanistic investigation [72]. Dependence on intact nasal mucosal health is a further variable: mucosal atrophy, chronic rhinitis, or anatomical variation could reduce absorption and CNS delivery, introducing pharmacokinetic heterogeneity between participants. No phase 3 trial has been completed. Translational readiness is moderate-to-high; the SNIFF phase 2 positive result justifies phase 3 investment, with device standardization and APOE4 stratification as the critical design elements [63, 64, 65, 72].

9. DISCUSSION

The body of evidence reviewed here reveals a mechanistically plausible, pharmacologically grounded case for antidiabetic drugs as neuroprotective agents in AD. Yet it also exposes a persistent gap between the consistency of preclinical findings and the limited conclusiveness of clinical trial data. Understanding why this gap exists is as important as cataloguing the positive findings. Across all drug classes, preclinical evidence is strongest at the mechanistic level and least translatable at the clinical outcome level. Liraglutide and semaglutide produce consistent amyloid and tau reductions in transgenic mice across multiple independent laboratories. However, the transgenic models used expressing familial AD mutations in young animals treated prophylactically do not reflect the typical clinical scenario: an elderly patient with sporadic, biomarker-confirmed AD presenting for treatment after years of pathological accumulation. This temporal and biological mismatch is the most fundamental challenge in the field. The SNIFF trial remains the most clinically informative completed study. Its positive primary endpoint in the 20 IU arm is meaningful, yet the 40 IU arm's failure to replicate this benefit creates interpretive uncertainty. A bell-shaped dose-response, previously described for hippocampal insulin signaling in vitro, could explain this pattern; alternatively, higher doses may generate negative feedback mechanisms that attenuate receptor-level signaling [72]. Future INI trials should include pharmacokinetic substudies measuring olfactory bulb and CSF insulin concentrations to resolve this ambiguity. The LINA trial's FDG-PET findings for liraglutide are objectively encouraging. Attenuation of posterior cortical metabolic decline, a surrogate biomarker with established prognostic relevance in a 12-month randomized trial, provides credible biological evidence of CNS activity. The absence of significant cognitive benefit likely reflects the trial's size and duration rather than drug inefficacy. The EVOKE and EVOKE+ trials of semaglutide, with their larger sample sizes, longer follow-up, and biomarker-stratified enrollment, represent the field's best near-term opportunity to determine whether GLP-1 RAs produce clinically meaningful cognitive benefit in AD. The TOMMORROW trial's failure for pioglitazone is instructive but not definitive. Enriching participants on genetic risk alone without amyloid biomarker confirmation inevitably includes individuals who will not develop AD during the trial window, diluting any real effect. At 0.8 mg/day, pioglitazone almost certainly did not achieve CNS concentrations sufficient for pharmacodynamic PPAR-γ engagement, an internal pharmacological problem that confounds the clinical interpretation entirely. Any future TZD trial in AD should incorporate CNS exposure confirmation and biomarker-confirmed preclinical AD population selection. The pharmacogenomic pattern across multiple trials, APOE4-negative patients responding more consistently, warrants a systematic mechanistic investigation. APOE4 may impair lipid-dependent GLP-1 receptor signaling, alter microglial cholesterol metabolism required for PPAR-γ function, or modify insulin receptor expression in hippocampal neurons through its known role

in synaptic lipid homeostasis [77]. Understanding this relationship could substantially improve patient stratification and trial design. Looking across the drug classes, intranasal insulin and GLP-1 receptor agonists currently offer the most clinically translatable evidence. They address multiple AD pathological pathways, have demonstrated biomarker-level CNS activity in humans, and have ongoing or planned phase 3 trials. Metformin's extensive epidemiological support and multi-target mechanistic profile make it a strong candidate for early intervention trials in prediabetic individuals with preclinical AD. DPP-4 inhibitors and TZDs, while mechanistically justified, require more robust clinical trial infrastructure before meaningful conclusions can be drawn.

10. CONCLUSION

Antidiabetic drugs are not incidentally relevant to Alzheimer's disease; they engage molecular pathways at the core of its pathogenesis. The biological convergence between T2DM and AD, formalized as Type 3 Diabetes, provides a rational scientific foundation for this therapeutic approach. Preclinical evidence across metformin, GLP-1 receptor agonists, DPP-4 inhibitors, thiazolidinediones, and intranasal insulin is mechanistically coherent and reproducible across multiple independent model systems. Clinical translation, however, remains incomplete. Inadequate power, heterogeneous populations, insufficient biomarker stratification, and, in some cases, pharmacological doses unlikely to achieve CNS target engagement have limited completed trials. These are correctable trial design failures, not inherent limitations of the therapeutic approach itself. The field now has the methodological tools to do better: amyloid PET and blood-based biomarkers enable biomarker-confirmed enrollment; pharmacogenomic stratification can identify APOE4-negative and insulin-resistant subpopulations most likely to benefit; PK/PD modeling can confirm CNS target engagement; and surrogate biomarker endpoints can detect early disease-modifying signals within feasible trial durations. The EVOKE trials and TAME-AD represent the next critical evidence-generation steps. Antidiabetic drugs will not replace disease-specific therapies for AD. They may, however, prove to be important components of a combination therapeutic strategy addressing the metabolic, inflammatory, and mitochondrial dimensions of neurodegeneration that anti-amyloid and anti-tau immunotherapies do not directly target. For the large and growing population of individuals with comorbid insulin resistance and AD risk, they may ultimately offer an accessible, affordable, and mechanistically grounded pathway to neuroprotection.

11. ABBREVIATIONS

Aβ, amyloid-beta; BDNF, brain-derived neurotrophic factor; ChAT, choline acetyltransferase; eNOS, endothelial nitric oxide synthase; BBB, blood-brain barrier; NF-κB, nuclear factor kappa-B; GLP-1R, GLP-1 receptor; NPY, neuropeptide Y; SDF-1α, stromal cell-derived factor-1 alpha; OCT, organic cation transporter; GLUT, glucose transporter; PP2A, protein phosphatase 2A; HPA, hypothalamic-pituitary-adrenal; tau-P, phosphorylated tau. CDR-SB, Clinical Dementia Rating -Sum of Boxes; FDG-PET, fluorodeoxyglucose positron emission tomography; MCI, mild cognitive impairment; NfL, neurofilament light chain; Aβ, amyloid-beta; CSF, cerebrospinal fluid; BID, twice daily; SC, subcutaneous; FA, fatty acids

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