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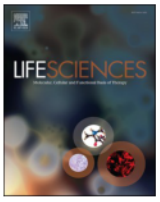

Repurposing antidiabetic drugs for Alzheimer's disease: A review of preclinical and clinical evidence and overcoming challenges

Jacky Tran, Sneh Parekh, Julia Rockcole, Danielle Wilson, Mayur S. Parmar *

Dr. Kiran C. Patel College of Osteopathic Medicine, Nova Southeastern University, Clearwater, FL, USA

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ABSTRACT

Repurposing antidiabetic drugs for the treatment of Alzheimer's disease (AD) has emerged as a promising therapeutic strategy. This review examines the potential of repurposing antidiabetic drugs for AD treatment, focusing on preclinical evidence, clinical trials, and observational studies. In addition, the review aims to explore challenges and opportunities in repurposing antidiabetic drugs for AD, emphasizing the importance of well-designed clinical trials that consider patient selection criteria, refined outcome measures, adverse effects, and combination therapies to enhance therapeutic efficacy. Preclinical evidence suggests that glucagon-like peptide-1 (GLP-1) analogs, dipeptidyl peptidase-4 (DPP4) inhibitors, metformin, thiazolidinediones, and sodium-glucose co-transporter-2 (SGLT2) inhibitors exhibit neuroprotective effects in AD preclinical models. In preclinical studies, antidiabetic drugs have demonstrated neuroprotective effects by reducing amyloid beta (Aβ) plaques, tau hyperphosphorylation, neuroinflammation, and cognitive impairment. Antidiabetic drug classes, notably GLP-1 analogs and SGLT2 inhibitors, and a reduced risk of dementia in patients with diabetes mellitus. While the evidence for DPP4 inhibitors is mixed, some studies suggest a potential protective effect. On the other hand, alpha-glucosidase inhibitors (AGIs) and sulfonylureas may potentially increase the risk, especially in those experiencing recurrent hypoglycemic events. Repurposing antidiabetic drugs for AD is a promising therapeutic strategy, but challenges such as disease heterogeneity, limited biomarkers, and benefits versus risk evaluation need to be addressed. Ongoing clinical trials in mild cognitive impairment (MCI) and early AD patients without diabetes will be crucial in determining the clinical efficacy and safety of the antidiabetic drugs, paving the way for potential treatments for AD.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the leading cause of dementia and may contribute to 60–70 % of cases. It affects over 6.9 million Americans aged 65 and older [1] and is part of a global trend that saw over 57 million people worldwide living with dementia [2,3]. This number is projected to rise to 13.8 million in the United States (US) by 2060 [1], and 153 million worldwide by 2050 [3], highlighting the urgent need for effective treatments. The increase in dementia cases, including AD, is a significant concern worldwide. AD is characterized by a gradual increase in cognitive impairment and a continuous decline in learning and memory over time. The neuropathological hallmarks of AD include intracellular neurofibrillary tangles (NFT) composed of hyperphosphorylated tau proteins and extracellular β-amyloid (Aβ) "senile" plaques [4–8]. Additional pathological changes include atrophy, neuronal loss, synaptic dysfunction, metabolic dysregulation, neuroinflammation, mitochondrial dysfunction, and reduced cholinergic function [9]. The economic impact of dementia, including AD, is also significant, with the total estimated worldwide cost above US $ 1.3 trillion and expected to rise to US$ 2.8 trillion by 2030. Developing therapeutics that target these underlying mechanisms remains a primary focus in AD research, and repurposing antidiabetic drugs for AD therapeutics could be a promising approach.

Currently, there are no curative treatments for AD, and available medications offer limited symptomatic control. The approved medications for AD by the Food and Drug Administration (FDA) include memantine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, and cholinesterase inhibitors, including donepezil, galantamine, and rivastigmine. Although these pharmacotherapies appear to slow aspects of cognitive impairment, the benefits are often marginal and non-sustained

* Corresponding author at: Department of Foundational Sciences, Dr. Kiran C. Patel College of Osteopathic Medicine, Nova Southeastern University, Tampa Bay Regional Campus, Clearwater, FL, USA.
E-mail address: mparmar@nova.edu (M.S. Parmar).

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Table 1
Antidiabetic drugs and their effects on Alzheimer's disease-related pathology in preclinical studies.

Drug class	Effects on AD-related pathology in preclinical studies
Glucagon-like peptide 1 (GLP-1) agonists	• Reduced Aβ levels, deposition, and aggregation [26–32] • Decreased tau hyperphosphorylation [29,33–40] • Prevented neuroinflammation [26–29,41–43] • Alleviated mitochondrial dysfunction [26–28,44] • Alleviated memory and cognitive impairment [27,32–34,44–52]
Biguanides (Metformin)	• Reduced Aβ levels and deposition [53–56] • Decreased tau hyperphosphorylation [55,57,58] • Prevented neuronal cell death [54,55] • Increased hippocampal neurogenesis [54] • Prevented neuroinflammation [54–56] • Alleviated memory and cognitive impairment [54–56]
Thiazolidinediones	• Reduced Aβ levels and deposition [59–66] • Reduced tau hyperphosphorylation [59,60,67] • Reduced neuroinflammation [61,64,66] • Reduced reactive oxygen species and oxidative stress [68] • Enhanced synaptic plasticity [59] • Prevented synaptic loss [62] • Alleviated memory and cognitive impairment [59–64,69,70]
Dipeptidyl peptidase-4 inhibitors	• Reduced Aβ levels and burden [71–76] • Reduced oxidative/nitrosative stress [72,76,77] • Reduced tau hyperphosphorylation and O-glycosylation [71,73–75,78] • Prevented neuroinflammation [71,72,75–78] • Alleviated memory and cognitive impairment [71–75,77–79]
Insulin (inhalation formulations)	• Reduced Aβ levels, production, and plaque formation [80–82] • Restored impaired brain insulin signaling [80,82] • Increased synaptic proteins [82] • Promoted hippocampal neurogenesis [80,83] • Alleviated memory and cognitive impairment [80,83,84]
Sodium-glucose cotransporter-2 (SGLT2) inhibitors	• Reduced Aβ levels, accumulation, and senile plaques [74,85] • Suppressed brain insulin resistance-induced tau hyperphosphorylation [86] • Prevented neuronal loss [85,86] • Inhibited synaptic damage [86] • Alleviated memory and cognitive impairment [74,85,86]
Alpha-glucosidase inhibitors	• Improved metabolic health [87] • Reduced Aβ aggregation [88] • Reduced oxidative stress and neuroinflammation [87] • Enhanced antioxidant enzymes [87] • Attenuated cognitive impairment [87,88] • Attenuated acetylcholinesterase and malondialdehyde [88] • Reduced pro-inflammatory cytokines (TNF-α, IL-1β, CRP) [88]
Sulfonylureas	• Restrained Aβ-induced memory deficit [89] • Inhibited hippocampal network activity [89] • Reestablished long-term synaptic plasticity balance [89] • Improved memory impairment in rats with T2DM and sporadic AD [90] • Reduced glucose and hippocampal inflammation [90] • Increased serum insulin levels [90] • Reduced serum inflammatory cytokines (TNF-α and IL-6) in the hippocampus of rats [90] • Decreased hippocampal hyperphosphorylated tau protein in Aβ-treated rats [91] • Improved learning and memory in Aβ-treated rats [91]

[10]. Monoclonal antibodies such as aducanumab, lecanemab, and donanemab effectively reduce Aβ pathology [11–13]. Aducanumab, lecanemab, and donanemab have received FDA approval, but in 2024, Biogen discontinued the production of aducanumab [12]. Aducanumab's therapeutic value is disputed due to the minimal improvement in clinical outcomes and the significant risk of amyloid-related imaging abnormality (ARIA), which includes edema and hemorrhage [12]. Furthermore, lecanemab, an approved medication, can cause adverse effects, ARIA, in patients more susceptible to severe disease, including women, homozygous carriers of APOE4, and those with comorbid vascular pathology [11,14]. It is important to note that traditional symptomatic treatments do not target key pathological processes that contribute to AD, such as neuroinflammation, oxidative stress, Aβ accumulation and toxicity, and NFT formation. Even the recently approved monoclonal antibodies, which show promise in clinical trials, lack the comprehensive overall targeting of these multiple pathophysiologies. These medications are typically prescribed once a patient is clinically diagnosed with MCI and AD. However, the ongoing search and evaluation of existing drugs that may have promising comprehensive targeting of all aspects of the disease pathology, coupled with their early intervention, could significantly reduce the risk of MCI and AD. Hence, the growing interest in repurposing existing drugs, including antidiabetic medication, for mitigating the early risk of MCI and AD is of clinical importance [15].

Emerging research evidence suggests compelling interconnecting pathological pathways between AD and type 2 diabetes mellitus (T2DM), a metabolic disorder characterized by insulin resistance [15,16]. These diseases share several pathophysiological mechanisms, including impaired insulin signaling, oxidative stress, mitochondrial dysfunction, and chronic inflammation [17,18]. Notably, 60–70% of individuals with T2DM experience cognitive impairment, underscoring the link between metabolic dysfunction and neurodegeneration [16,19,20].

Both AD and T2DM exhibit disruptions in insulin signaling pathways in the brain, which are crucial for regulating various neuronal functions, including glucose metabolism, synaptic plasticity, Aβ clearance, and tau regulation [16,21]. Chronic low-grade inflammation, a hallmark of T2DM, also plays a pivotal role in AD pathogenesis, contributing to impaired brain insulin resistance, neuroinflammation, Aβ accumulation, tau hyperphosphorylation, and neuronal damage [18,22,23].

Furthermore, increased oxidative stress and mitochondrial dysfunction, resulting from insulin and IGF-1 resistance in the brain, have been implicated in both T2DM and AD. These factors activate pro-apoptotic, pro-inflammatory, and pro-APP-Aβ cascades, affecting tau protein expression and metabolism and leading to cellular damage in the brain [17,18,23,24]. This shared pathophysiology not only underscores the connection between AD and T2DM but also has significant implications for potential therapeutic strategies. It highlights the potential of repurposing anti-diabetic drugs, specifically those with an insulin-sensitizing effect and other direct actions independent of the insulin-signaling mechanism, as novel therapeutic strategies for AD [25].

This review aims to comprehensively evaluate the preclinical and clinical evidence for various antidiabetic drugs, including biguanides (metformin), sodium-glucose cotransporter 2 inhibitors (SGLT2i), dipeptidyl peptidase 4 inhibitors (DPP4i), glucagon-like peptide-1(GLP-1) analogs, insulin, thiazolidinediones, alpha-glucosidase inhibitors (AGIs), and sulfonylureas in the context of dementia, especially MCI and AD. By examining their impact on AD pathology and clinical progression, we aim to shed light on the potential of these drugs as novel therapeutic options for this devastating neurodegenerative disease.

2. Overview

Table 1 summarizes the impact of various antidiabetic drugs on key pathological processes in AD, as observed in preclinical models. Fig. 1 provides a visual representation of the potential therapeutic targets of these medications within the complex pathophysiology of AD.

2.1. Glucagon-like peptide 1 analogues

Glucagon-like peptide 1 (GLP-1) analogs, also called incretins, are a class of antidiabetic drugs that include exendin-4, liraglutide, lixisenatide, and semaglutide. They mimic the action of the GLP-1 hormone. Secreted by intestinal L cells postprandially, GLP-1 stimulates insulin secretion from pancreatic β-cells and inhibits glucagon secretion. GLP-1 is metabolized and degraded by the dipeptidyl peptidase-4 (DPP4) enzyme and excreted renally. Incretin mimetic medications can bind to the GLP-1 receptor and resist metabolism by the DPP4 enzyme, allowing increased insulin secretion, decreased glucagon release, and slowed gastric emptying. Importantly, GLP-1 can cross the blood-brain barrier [92–94] and bind to GLP-1 receptors expressed by neurons, particularly pyramidal neurons in the hippocampus and neocortex and Purkinje cells in the cerebellum [95–97].

Several preclinical studies (in vivo) have reported the beneficial effects of GLP-1 receptor agonists (GLP-1 RA), GLP-1/GIP, and GLP-1/GIP/glucagon analogs in mitigating AD pathophysiology in AD mouse models through various mechanisms [26–29,31–35,37–44,46,49,50,52,92,94,95,98–115]. GLP-1 RAs reduced Aβ levels, deposition, and aggregation [26–32]. Furthermore, GLP-1 RAs reduced tau hyperphosphorylation [29,33–40], neuroinflammation [26–29,41–43], mitochondrial dysfunction [26–28,44], and synaptic loss [32], while improving hippocampal neuronal numbers [49] and cognitive function [27,32–34,44–52]. GLP-1 RAs have been shown to protect against oxidative stress, enhance neurogenesis, and favorably modulate key signaling pathways (e.g., Akt/GSK-3β/β-catenin). At the molecular level, preclinical studies highlight that GLP-1 binds to its receptor in the brain and activates adenylyl cyclase, leading to increased levels of cAMP, PKA, and other downstream kinase modulators, including the PI3K, MAPK, AKT/PKB, and GSK-3β pathways. The modulatory effects of these pathways lead to a cascade of neuroprotective benefits. GLP-1 mimetics have been shown to preserve mitochondrial dysfunction in astrocytes by activating the cAMP/PKA pathways, inhibiting Aβ deposition. The preserved function of astrocytes in the central nervous system (CNS) also helps maintain nutrition, homeostasis, and synaptic plasticity [26–28]. Downstream activation of the PI3K/AKT cascade by GLP-1 analogs increases the expression of superoxide dismutase, an antioxidant, inhibiting oxidative stress and preventing apoptosis and chronic inflammation [33–35]. This also helps prevent the activation of GSK-3β,

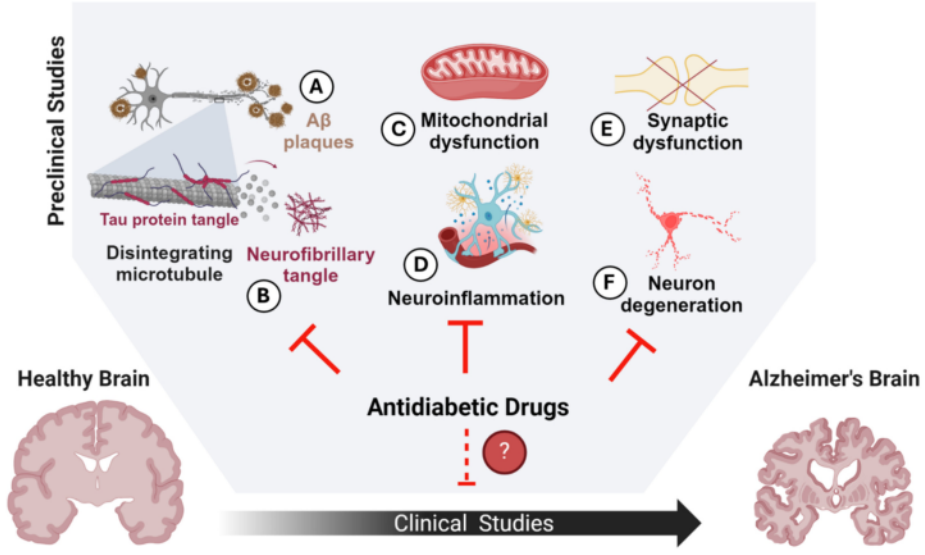

Fig. 1. The diagram illustrates the potential therapeutic effects of antidiabetic drugs on the pathophysiology of AD. Preclinical studies suggest that these medications can target multiple pathological hallmarks of AD in the brain, including A) amyloid-beta (Aβ) plaques — accumulation of Aβ plaques is a key feature of AD. Antidiabetic drugs may reduce Aβ plaque formation and aggregation; B) neurofibrillary tangles — hyperphosphorylated tau aggregates disrupt neuronal function. Antidiabetic drugs may inhibit tau protein phosphorylation and aggregation, thus preventing tangle formation; C) mitochondrial dysfunction — impaired mitochondrial function contributes to neuronal damage. Antidiabetic drugs may improve mitochondrial function and energy metabolism; D) neuroinflammation — chronic inflammation in the brain exacerbates AD progression. Antidiabetic drugs may possess anti-inflammatory properties that mitigate neuroinflammation; E) synaptic dysfunction — loss of synapses disrupts communication between neurons. Antidiabetic drugs may enhance synaptic plasticity and protect synapses from degeneration; and F) neuron degeneration and loss — the ultimate consequence of AD pathophysiology is neuronal loss. Antidiabetic drugs may promote neuronal survival. While these preclinical findings are promising, the exact mechanisms by which antidiabetic drugs may exert their beneficial effects on the pathophysiology of AD are not yet fully understood (indicated by the "?"). Clinical studies are underway to investigate the efficacy and safety of these medications in AD patients, with the goal of translating preclinical findings into effective treatments for this devastating neurodegenerative disease.

a pathway linked to tau hyperphosphorylation in neurons, leading to AD [16]. Inhibition of this pathway and other downstream effects of activation of the cAMP/PKA pathway suggests that incretins could have benefits in combating the learning and memory impairments seen in AD [33–35].

Given their receptor distribution and promising preclinical evidence, GLP-1 analogs have garnered significant interest for their potential neuroprotective role in AD. This interest has led to recent human randomized, placebo-controlled, double-blind trials offering mixed but encouraging results. In human studies, a preliminary trial with liraglutide involved 38 AD patients, where each participant underwent ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) and ^{11}C-labeled Pittsburgh Compound-B (^{11}C-PIB) scans both before starting the trial and after 6 months of liraglutide to assess regional cerebral glucose metabolic rate (CMRGlc) and amyloid deposition, respectively. Results indicated that liraglutide helped maintain cerebral glucose metabolism levels but did not significantly impact cognitive function scores or amyloid levels [116]. An 18-month exploratory trial examined the effects of exenatide on AD. The results showed that exenatide treatment was safe and well-tolerated, with similar neuropsychological and MRI (Magnetic Resonance Imaging) outcomes observed in both exenatide-treated and placebo groups. However, the study revealed a reduction in $A\beta_{42}$ levels in extracellular vesicles among participants receiving exenatide compared to baseline and placebo recipients after 18 months [116]. This suggests a potential for exenatide to mitigate brain amyloidosis, which warrants further investigation in AD. The trial concluded prematurely, which limited its statistical power to achieve predefined outcomes. A phase 2 double-blind placebo-controlled trial in 2021 demonstrated that liraglutide-treated patients had improved cognitive function compared to patients in the placebo arm [117]. Furthermore, an analysis of pooled data from three double-blind RCTs (Randomized Controlled Trials) with a sample size of 15,000 patients showed that treatment with GLP-1 RAs was associated with decreased dementia development in T2DM patients [118]. However, in a 2019 double-blind placebo-controlled study of 32 patients with mild cognitive impairment (MCI), the functional decline was prevented compared to placebo, but there was no cognitive improvement [119]. In a systematic review and meta-analysis evaluating newer antidiabetic drugs (GLP1-RAs, DPP4i, and SGLT2i) and the risk of dementia, GLP1-RAs were associated with a reduced risk of all-cause dementia in people with T2DM [120]. Similarly, in the latest systematic review and meta-analysis evaluating the effect of diabetes on the risk of dementia, along with other antidiabetic drugs (metformin, thiazolidinediones, pioglitazone, and SGLT2 inhibitors), GLP-1 RAs were associated with a significantly reduced risk of dementia [121]. Two phase 3 studies (EVOKE and EVOKE plus) evaluating the efficacy of semaglutide in treating early AD in amyloid-positive patients are underway (ClinicalTrials.gov Identifier: NCT04777396, NCT04777409) [122]. These studies will provide additional information to clarify the role of GLP-1 agonists in AD management.

No human observational studies, blood/plasma, cerebrospinal fluid (CSF), or postmortem tissue analyses have reported the impact of GLP-1 RAs on Aβ and tau pathology. It would be valuable to investigate whether patients who have diabetes, have been on GLP-1 RAs for an extended period of time, and later develop AD have reduced Aβ and NFT pathophysiology, as well as a reduction in inflammation and mitochondrial dysfunction, compared to those who do not use GLP-1 RAs.

2.2. DPP4 inhibitors

Dipeptidyl peptidase-4 inhibitors are antidiabetic drugs that include sitagliptin, saxagliptin, gemigliptin, linagliptin, alogliptin, and vildagliptin. DPP4i are considered for therapy in patients with contraindications or intolerance to first-line diabetic medications such as metformin. DPP4i increases incretin hormone levels, restoring insulin balance and raising GLP-1 levels. Interestingly, increased GLP-1 in the brain has been linked to neuroprotective effects, as mentioned in the above section. This connection suggests that DPP4i holds promise as a potential disease-modifying drug for diabetic patients with AD.

Extensive preclinical studies have demonstrated the potential benefits of DPP4i in mitigating AD-related pathophysiology [71–75,77–79]. DPP4i reduced $A\beta_{42}$ accumulation [71–76], tau hyperphosphorylation [71,73–75,78] and O-glycosylation [73], amyloid burden [71], oxidative/nitrosative stress [72,76,77], and neuroinflammation [71,72,75–78]. These medications have also been reported to reverse cognitive impairment and improve spatial reference memory [71–75, 77–79], in addition to improving synaptic plasticity by enhancing synapse protein levels [73]. These reported potential benefits of DPP4i have been associated with augmenting GLP-1 levels [71–73,75–79], increasing cerebral perfusion [79], and by enhancing brain insulin signaling [72,74,77] through altering the brain's insulin resistance (BIR) via the insulin receptor substrate-1 (IRS-1) [72]. At the molecular level, DPP4i were reported to improve GLP-1 signal transudation by increasing the phosphorylation of PI3K (p85)/Akt (S473), ERK1/2, and GSK-3β (S9) and decreasing the phosphorylation of JNK1/2 [73]. In addition, DPP4i decreased Aβ accumulation by increasing insulin-degrading enzymes (IDE) [74].

Evidence suggests that DPP4i offers potential benefits in mitigating cognitive decline and the risk of dementia in human studies [120,123,124]. DPP4i have been shown to reduce the risk of all forms of dementia [120,123,124], including AD outcomes [123,124], which has been noted in a few clinical observational and randomized control studies. In a retrospective longitudinal study, it was reported that in older patients with T2DM affected by MCI, DPP4i (vildagliptin, sitagliptin, or saxagliptin) administration for a treatment period of 2 years improved glucose control and protected against worsening cognitive functioning [125]. Studies investigating vildagliptin indicate a stabilization of cognitive performance, measured by the Mini-Mental State Examination (MMSE), in elderly diabetic patients with MCI [126]. Further randomized controlled trials are needed to confirm the findings regarding sitagliptin. However, preliminary data suggests that its use for 6 months, compared to metformin use for the same duration, may be associated with improvements in cognitive function [127]. Additionally, DPP4i combined with metformin may offer greater protection against AD than metformin combined with sulfonylureas. The meta-analysis of seven studies suggested a potential association between DPP4i use and a decreased risk of all-cause dementia and vascular dementia (VD) in patients with T2DM. However, the study could not conclude a similar benefit in preventing AD [120]. Another systematic review and network meta-analysis reported an association between DPP4i use and a modestly lower risk of dementia in patients with T2DM. Evidence suggests that DPP4i are the fourth best among SGLT2i, GLP-1 RA, and thiazolidinediones in terms of delayed cognitive impairment, dementia, and AD outcomes [123]. Overall, the use of DPP4i medications has positive effects on glycemic control, which may be linked to improved cognitive function. In addition, DPP4i decreases the incidence of hypoglycemic events, further protecting against associated cognitive damage. This highlights the potential of DPP4i as a therapeutic option to address cognitive decline in the context of diabetes management. Interestingly, in a recent systematic review and meta-analysis, which analyzed 100 reviews and 27 cohort/case-control studies totaling 3,046,661 participants, no significant effect was found for dipeptidyl peptidase-4 inhibitors on the risk of dementia. The discrepancy in these findings regarding DPP4i can be attributed to the exclusion studies that lacked sufficient data to calculate relative risk [121]. This highlights the imperative need to conduct future longitudinal studies with extended follow-up durations and standardized assessment methods to comprehensively characterize the relationship between DPP4i treatments and the risk of dementia/AD. Such studies are essential to better understand these treatments' potential effects and support effective decision-making in clinical practice.

Currently, there is no data from human studies, including blood and

plasma analyses, CSF analyses, or postmortem tissue analyses, on the effect of DPP4i treatment on Aβ and tau pathology linked to AD. However, multiple observational studies have indicated that DPP4i therapy may reduce the risk of dementia, including AD. Therefore, it would be beneficial to explore whether DPP4i treatment can alleviate the pathophysiology of AD in early AD among amyloid-positive patients without any preexisting diabetic conditions.

2.3. Biguanides (Metformin)

Biguanides are synthetic medications derived from guanidine, where two guanidine molecules are linked with a nitrogen atom [128]. Metformin is a prominent and widely used biguanide for its antihyperglycemic properties in treating T2DM. Metformin is currently the only biguanide marketed in the United States, United Kingdom, Canada, and Australia to treat T2DM and is the first-line drug in T2DM treatment [129]. Metformin increases insulin sensitivity in the liver to help lower blood glucose levels. Other beneficial effects noted through metformin treatment include weight loss [130,131], reduced risk of cardiovascular disease [130,132,133], and the novel ability to reduce cognitive decline and AD.

The general mechanism of action of metformin is to inhibit gluconeogenesis, the opposite of the action of glucagon, which allows glucose uptake in skeletal muscle [134]. Metformin stimulates adenosine monophosphate (AMP)–activated protein kinase (AMPK) [134]. AMPK is activated primarily during metabolic stress, such as hypoxia and glucose deficiency [135]. When metformin accumulates in hepatocytes, it results in a low-energy state, leading to activation of AMPK. AMPK inhibits gluconeogenic gene transcription along with lipogenesis, thus increasing the insulin sensitivity of peripheral tissues [134]. A critical role of AMPK is in regulating tau phosphorylation and Aβ production, two of the critical biomarkers seen in AD [136]. Due to the relationship between T2DM and AD and the unique mechanism of action of metformin, metformin is another drug in which research has been carried out to see if there is any potential benefit for disease reduction in AD patients and improvement in overall cognition in dementia.

Research in animal models offers insights into the potential ways metformin could address AD pathology. Animal studies have demonstrated the potential benefits of metformin. Metformin has a multifaceted impact on the pathophysiology of AD. Its influence on Aβ deposition is twofold: while it can increase Aβ production through its molecular mechanism, it also has a positive and beneficial effect by aiding Aβ clearance when considering relevant factors. In mouse models, metformin treatment reduced tau phosphorylation and attenuated Aβ accumulation, mitigating characteristic AD-associated changes [57,58]. Although preclinical studies suggest promising results, translating these benefits into human studies remains complex. In addition, it is inconsistent, highlighting the need for further investigation and research. Some promising studies have highlighted that metformin has been found to improve executive functioning, learning, memory, and total recall compared to placebo [137,138]. Additionally, some studies suggest that metformin could reduce the risk of dementia. When used with sulfonylureas, it decreased the risk of dementia in patients with DM2 by 35% over an 8-year period [139]. In addition, metformin use alone has been associated with a lower subsequent risk of dementia than sulfonylureas [140].

Although some human studies have shown promising results, the potential benefits of metformin for AD require further validation due to conflicting evidence highlighting the complexity of metformin's role in AD. In a randomized, placebo-controlled trial with 80 non-diabetic participants with MCI, metformin showed positive effects on memory after 12 months of daily use. However, no differences were observed in Alzheimer's Disease Assessment Scale-cognitive subscale 12 (ADAS-Cog12), CSF, Aβ42, and cerebral glucose metabolism [138]. The study concluded that a larger trial is needed to evaluate metformin efficacy and cognitive safety in prodromal AD. Similarly, another placebo-controlled crossover study was conducted to test the effects of metformin on CSF, neuroimaging, and cognitive biomarkers. Twenty non-diabetic subjects with MCI or mild dementia due to AD were randomized to receive metformin and then a placebo for 8 weeks each or vice versa. The study reported that metformin was safe, well tolerated, and measurable in the CSF. The findings suggested that metformin treatment was associated with improved executive functioning, with trends suggesting improved learning/memory and attention. However, no significant changes in cerebral blood flow were observed. Post hoc analyses did indicate an increase in orbitofrontal cerebral blood flow. Metformin treatment did not significantly affect Aβ42, total tau, p-tau in CSF, language, or motor speed [137].

A cohort study of 4651 diabetic patients indicated that long-term metformin administration (12-year follow-up) could increase the risk of all-cause dementia, vascular dementia, and AD [141]. These findings are consistent with previous results [142]. Furthermore, long-term use of sulfonylureas, thiazolidinediones, or insulin has been associated with a lower AD risk than metformin [143]. In a systematic and meta-analysis study evaluating nineteen studies (including cross-sectional, cohort, and clinical trials), it was concluded that metformin does not have a significant effect on improving cognitive function or protecting against any type of dementia, including VD and AD, and cognitive impairment as well [144]. In separate systematic reviews and meta-analyses of clinical observational studies (10 studies involving 229,110 participants) evaluating the association between metformin and the risk of developing AD, it was concluded that metformin does not reduce the risk of AD. Interestingly, this study reported an increased risk of AD in the Asian population among metformin users compared to those who did not [145]. Contrary to the above meta-analysis, a recent systematic review and meta-analysis found that metformin may offer protection against dementia. However, this effect was primarily observed in studies from the United States and Western countries. The impact in Eastern populations was insignificant, highlighting the need for more comprehensive research to understand the potential geographical differences in metformin's impact on dementia risk [121]. Among ongoing debates based on findings as to whether metformin mitigates or does not mitigate cognitive impairment and AD risk, a recent study provides strong evidence to support the protective effects of metformin against dementia in elderly T2DM patients [146]. Using a time-dependent Cox hazards model, the study demonstrated a significant reduction in the risk of dementia among metformin users. Importantly, this protective effect was dose-dependent, with higher daily intensities and cumulative doses of metformin linked to even greater reductions in risk [146]. These findings suggest that metformin could play a valuable role in preventing diabetes-related cognitive decline and dementia, especially in older people with T2DM.

Insufficient study length or limited sample sizes might explain the lack of convincing evidence in numerous studies, conflicting meta-analyses, and trials. Therefore, broader cohort studies with longer durations of metformin use and larger study groups are necessary to definitively determine the effects of metformin in managing and preventing the risk of dementia and AD.

2.4. Thiazolidinediones

Thiazolidinediones, such as rosiglitazone and pioglitazone, are commonly used to improve glycemic control in adults with T2DM and are recognized as peroxisome proliferator-activated receptor gamma (PPARγ) agonists. Several preclinical and human studies suggest that these medications can treat neurodegenerative diseases, including AD, by improving neuropathology and cognitive outcomes.

In preclinical studies, thiazolidinediones, such as pioglitazone and rosiglitazone, have shown potential benefits in mitigating AD-related pathophysiology. Stimulation of PPARγ has been demonstrated to decrease Aβ levels and deposition [59–66], increase Aβ phagocytosis and clearance [60,64,147], lower tau hyperphosphorylation and

aggregation [59,60,67], suppress neuroinflammation [61,64,66], enhance synaptic plasticity [59], reduce synaptic loss [62], and rescue memory impairment [59–64,69,70]. However, a recent study with long-term pioglitazone treatment in a tau P301S animal model did not alter tau pathology, in contrast to several studies indicating that thiazolidinedione medications reduce tau hyperphosphorylation and aggregation [148]. The beneficial effects of thiazolidinediones medications in the mitigation of AD-associated pathologies have been linked to increased expression of low-density lipoprotein receptor-related protein 1 (LRP1) [63], inhibition of Cdk5 activity through reduction in p35 protein levels [69], downregulating Cdk5 expression [65], inhibition of PPARγ phosphorylation [65], increased insulin-degrading enzyme [65], decreased BACE1 expression [65,66], and reduction in APP production [65].

Despite the promising results in preclinical studies, the potential benefits of thiazolidinediones for human AD patients require further validation. Pioglitazone has been evaluated in a few clinical studies in humans to reduce the risk of dementia and/or delay in the onset of AD [68,149]. The neuroprotective efficacy of pioglitazone was tested in a study on participants with T2DM and mild AD, resulting in improved cognition and regional cerebral blood flow (rCBF) and disease stabilization [150]. The single-photon emission computed tomography (SPECT) study demonstrated that the pioglitazone group improved rCBF in the parietal lobe. On the contrary, the control group showed no significant changes in rCBF in any brain region after 6 months of treatment. Pioglitazone treatment was also correlated with improvements in scores on the MMSE, Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-J-cog), and the Wechsler Memory Scale-Revised (WMS-R). At the same time, the control group showed worsened scores on the ADAS-J-cog after 6 months of treatment. In a large prospective cohort study that analyzed the association of pioglitazone and dementia incidence in 145,928 subjects ≥60 years of age who, at baseline, were free of dementia and insulin-dependent diabetes mellitus, long-term use of pioglitazone treatment was associated with a reduced risk of dementia by 47% over 5 years relative to nondiabetics [149]. Patients with diabetes without pioglitazone treatment were observed to have a 23% increase in dementia risk [149]. However, a subsequent phase 3 study (NCT01931566, TOMORROW) that investigated whether a biomarker-based algorithm (BRAA) could accurately predict individuals at high risk of developing MCI due to AD failed to confirm initial findings on 3494 participants between 65 and 83 years of age with normal cognitive at baseline, randomly assigned to placebo or low-dose pioglitazone (0.8 mg) daily, with a 5-year follow-up period [68]. The results showed that pioglitazone failed to delay the onset of MCI due to AD relative to placebo, even in cognitively intact individuals deemed at high risk for developing AD based on their age and APOE and TOMM40 genotypes [68]. In a recent systematic review and meta-analysis that investigated the impact of diabetes on the risk of dementia, pioglitazone was found to have a protective effect on the overall risk of dementia. It was also observed that the lower risk ratio for pioglitazone compared to other thiazolidinediones could be due to the greater adverse effects associated with rosiglitazone [121]. Similarly, in a meta-analysis in which pioglitazone was compared to other antidiabetic drugs, placebo, or a diabetic diet for a minimum duration of 6 months, pioglitazone initially did not show an improvement in ADAS-J-Cog scores [151]. However, a positive effect was observed when one study was excluded by conducting a sensitivity analysis [151]. The Wechsler Memory Scale-Revised logical memory I (WMS-R) scores showed improvement in the group taking pioglitazone [151].

Some contradictory findings from clinical trials, observational studies, and meta-analyses further highlight the imperative need to conduct future longitudinal studies with extended follow-up durations and standardized assessment methods to comprehensively characterize the relationship between thiazolidinedione treatments and the risk of dementia/AD. Such studies are essential for better understanding the potential effects of thiazolidinedione treatments and for supporting effective clinical decision-making.

2.5. Insulin

Insulin is a peptide hormone the pancreas produces that regulates blood sugar levels. Upon release, insulin binds to alpha and beta cell receptors, which are linked by two disulfide bonds and form a heterotetrameric complex. The binding of insulin to receptors results in a conformational change that triggers the activation of tyrosine kinase by ATP and subsequent receptor autophosphorylation. This event initiates a cascade of signaling pathways that stimulate glucose uptake into muscle and fat cells through increased glycolysis and glucose transport while inhibiting gluconeogenesis and glycogenolysis. Insulin can be classified according to its duration of action or origin. Primary classifications of insulin include short-acting, rapid-acting, intermediate-acting, mixed-insulin, and long-acting insulin. Additionally, insulin can be derived from animal insulin, synthetic insulin, or insulin analogs.

In the CNS, insulin plays a significant role, including neuroprotection mediated by mitigation of oxidative stress, mitochondrial damage, and inflammation by INS-related PI3K/Akt and MAPK signaling pathways. Insulin receptors are found in regions such as the hippocampus, amygdala, cerebral cortex, and olfactory bulb, areas crucial for learning and memory [16]. Research indicates that dysregulation of insulin signaling, including insulin deficiency and/or impaired insulin function and/or reduced insulin receptor sensitivity, may contribute to the neuropathology underlying cognitive impairment and AD as observed in metabolic disorders, such as T2DM [16,152–154]. Insulin deficiency and/or dysfunction in insulin signaling in the CNS can promote the formation of the toxic $A\beta_{42}$ conformer [84], increase soluble Aβ [154], enhance Aβ deposition [155], impair Aβ clearance, and cause tau phosphorylation [16,84,156,157], neuroinflammation, and memory impairment [16,84,153–155].

Several preclinical studies have shown that correcting insulin signaling dysfunction in the CNS can mitigate Aβ and tau pathology, improve synaptic plasticity, and reduce neuroinflammation and cognitive impairment plasticity [152]. Delivering insulin directly into the CNS is challenging. Therefore, alternative methods such as intranasal delivery are being explored to potentially improve insulin signaling and resistance, as well as modulate the cognitive impairment associated with AD. In preclinical and clinical trials, intranasal insulin administration resulted in a wide distribution throughout the brain, with minimal systemic circulation observed when using optimal formulations.

Preclinical studies in animal models of experimental AD and brain insulin resistance demonstrated the potential benefits of intranasal insulin in mitigating AD neuropathology, improving cognitive impairment, and reversing insulin resistance in the brain [80,81,83,84]. Intranasal insulin improved cognition and memory in the APPswe/PS1dE9 AD mouse model. It reduced Aβ production and plaque formation by enhancing nonamyloidogenic processing and compromised amyloidogenic processing of amyloid precursor protein (APP) and from a reduction in apolipoprotein E protein, which is involved in Aβ metabolism [80]. Treatment also restored impaired brain insulin signaling [80] by inhibiting the c-Jun N-terminal kinase activation, which plays a pivotal role in insulin resistance and AD pathologies [80]. In addition, the treatment promoted hippocampal neurogenesis. In a rat and mouse model injected with streptozocin (STZ) as an experimental model of AD and/or brain insulin resistance, intranasal insulin administration showed reduced Aβ levels [81] and restoration of learning and memory functions along with enhanced hippocampal neurogenesis [83]. Intranasal insulin delivery also corrected the insulin signal pathway by activating the IRS-1-PI3K-Akt-GSK3β pathway and increasing the brain insulin levels [83]. In the latest study involving Aβ-induced Alzheimer's-like disease in the rat model, intranasal insulin intake and exercise improved memory function [84]. Overall, intranasal insulin treatment has shown promising evidence in preclinical studies to reduce AD neuropathology and improve cognitive impairment through distinct molecular mechanisms. These mechanisms include increasing brain insulin levels, activating the insulin signaling pathway, enhancing

hippocampal neurogenesis, and reducing Aβ production and clearance.

Several studies in clinical trials have evaluated intranasal insulin in patients with MCI or AD to have therapeutic benefits of cognitive improvement without the risk of peripheral hypoglycemia [158–169]. These studies also evaluated changes in the Aβ peptide ($A\beta_{40}$ or $A\beta_{42}$), tau levels, neuroinflammatory markers, and other biomarkers in plasma and CSF associated with intranasal insulin treatment [159,162,166,168,170]. Initial clinical trials suggested a potential improvement in verbal memory retention and recall [158–160], general cognition as assessed by the ADAS-cog score [162,170], functional abilities as assessed by the ADCS-ADL scale for AD adults [162], delayed story memory recall [163], verbal working, and visuospatial working memory [164]. However, contrary to studies that indicate improvement in memory and cognition, longer-term clinical trials have shown less conclusive results. For example, a 12-month randomized (1:1) double-blinded clinical trial study found no significant changes in primary outcomes such as ADAS-cog-12 scores or CSF outcomes with intranasal insulin treatment [166]. Another study evaluating the safety and efficacy of rapid-acting intranasal glulisine in subjects with amnestic MCI or mild probable AD found no significant differences in ADAS-Cog13, Clinical Dementia Rating Sum of Boxes (CDR-SOB), or Functional Activities Questionnaire (FAQ) scores between treatment groups at 3 and 6 months, indicating no enhanced effects on cognition, function, or mood. However, the study noted that the ability to detect significance was limited by the number of subjects enrolled and the study duration [167].

It is important to note that differences in sex and ApoE genotype in MCI or AD can show differential dose-response curves after intranasal insulin administration [160,163–165]. Following intranasal insulin administration, changes in CSF biomarkers were also observed. Changes in memory and function were associated with changes in the $A\beta_{42}$ level and tau protein-to-$A\beta_{42}$ in the CSF [162]. In a Phase 2 trial, intranasal insulin showed potential as AD treatment as treatment was associated with positive changes in CSF biomarkers and slower disease progression in patients with MCI or AD [168]. Specifically, the insulin-treated group exhibited altered levels of CSF immune, inflammatory, and vascular markers, including increased interferon-γ and eotaxin and decreased interleukin-6 [168]. These changes contrasted with the placebo group's typical marker progression associated with AD. The findings suggest that intranasal insulin could trigger a compensatory immune response, contributing to its therapeutic benefits for AD patients [168]. Intranasal insulin treatment has also been shown to change neuronal-enriched EV biomarkers of insulin resistance, indicating the target engagement of intranasal insulin and thus allowing the tracking of treatment-associated cognitive changes in AD [170]. In the study, in participants with amnestic MCI or probable AD, in a 4-month duration trial of intranasal insulin treatment, extracellular vesicle (EV) biomarkers of insulin resistance (pS312-IRS-1, pY-IRS-1) showed strong positive correlations with ADAS-Cog changes, especially in ApoE ε4 non-carriers [170]. There was also a significant reduction in changes in white matter hyperintensity volume seen in the deep and frontal regions following 12 months of intranasal insulin treatment [169].

Clinical trials evaluating intranasal insulin in patients with MCI or AD have yielded mixed results. Some studies suggest improvements in verbal memory, general cognition, and functional abilities, while others did not find significant differences in primary outcomes. Clinical trials have evaluated intranasal formulations with varying doses and treatment periods to investigate their impact on AD neuropathology and cognition. However, the results have been inconclusive. More research is needed to evaluate the neuroprotective effects of intranasal insulin administration, particularly in larger groups of patients with MCI and AD, and over an extended period, with defined dose concentrations.

2.6. Sodium-glucose cotransporter-2 inhibitors

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are a type of antidiabetic medication that works differently from most other antidiabetic drugs. They lower glucose levels by causing the kidneys to excrete glucose in the urine. Cells that line the proximal tubule contain molecules called the sodium-glucose-linked transporter on the luminal side, which allow sodium and glucose to move from the interstitial fluid to the blood. SGLT2i prevent this movement and absorption of glucose, which reduces glucose levels in the body.

Several preclinical studies have demonstrated the potential benefits of SGLT2i in mitigating AD-related neuropathophysiology and improving recognition dysfunction in AD rodent models [74,85,171,172]. In a mixed murine model of AD and T2D (APP/PS1 × d/db), empagliflozin treatment was shown to significantly reduce Aβ levels, decrease the density of senile plaques in the cortex and hypothalamus, decrease neuronal loss, and improve cognition [85]. In a mouse model with T2D-AD using a high-fat diet with a single dose of STZ, empagliflozin treatment improved hippocampal-dependent learning, memory, and cognitive function [74]. Empagliflozin treatment also reduced tau phosphorylation and Aβ accumulation while enhancing brain insulin signaling. The reduction in tau phosphorylation by empagliflozin was achieved through the angiotensin-converting enzyme-2/angiotensin (1-7)/mitochondrial assembly receptor axis [74]. Dapagliflozin, in particular, showed reduced tau phosphorylation and β-site amyloid precursor protein cleaving enzyme 1 (BACE1) in an ovariectomized/d-galactose AD rat model [171]. The beneficial effects of dapagliflozin are associated with LKB1/AMPK/SIRT1 signaling as the main contributor to the reduction in AD pathology [171].

Evidence suggests that SGLT2i offers potential benefits in mitigating cognitive decline and the risk of dementia in human studies [173–175]. In a nested case-control study within a cohort of all 176,250 patients registered with T2DM in the Danish National Diabetes Register, the use of SGLT2i, along with DPP4i and GLP1 analogs, was associated with lower odds of dementia with a gradual decrease in odds of dementia for each increase in the defined daily dose [154]. In another population-based cohort study, SGLT2i, compared to DPP4i, were associated with a lower risk of dementia over a mean follow-up of 2.8 years from cohort entry [175]. Among the SGLT2i, dapagliflozin exhibited the lowest risk, followed by empagliflozin; however, canagliflozin showed no association [175]. In a longitudinal study of patients with T2DM, the use of SGLT2i for $\geq$3 years was associated with improved cognitive scores [174]. This improvement was seen across multiple domains, including global cognition, language, and executive function [174]. In a systematic review and meta-analysis evaluating newer antidiabetic drugs (GLP1-RAs, DPP4i, and SGLT2i) and the risk of dementia, three studies found that users of SGLT2i had a lower risk of all-cause dementia than non-SGLT2i users and were associated with a lower risk of all-cause dementia in people with T2DM [120]. Similarly, in the latest systematic review and meta-analysis evaluating the effect of diabetes on the risk of dementia, together with other antidiabetic drugs (metformin, thiazolidinediones, pioglitazone, and GLP1-RAs), SGLT2i were associated with a significantly reduced risk of dementia [121].

Currently, there is no data from human studies, including blood and plasma analyses, CSF analyses, or postmortem tissue analyses, on the effect of SGLT2i treatment on Aβ and tau pathology linked to AD. Therefore, it would be beneficial to explore whether SGLT2i treatment can alleviate the pathophysiology of AD in early AD among amyloid-positive patients without any preexisting diabetic conditions.

2.7. Alpha-glucosidase inhibitors

Alpha-glucosidase inhibitors (AGIs) are oral antidiabetic drugs that delay carbohydrate digestion and absorption in the small intestine. These drugs are primarily used to manage T2DM by reducing postprandial hyperglycemia. However, recent research in preclinical AD animal models has revealed their potential in mitigating AD pathophysiology through various mechanisms, primarily by improving metabolic health and reducing Aβ aggregation, oxidative stress, and neuroinflammation [87,88].

In 3xTg mice, a model of AD, acarbose treatment not only improved glycemic control and reduced body weight and adiposity but also ameliorated cognitive deficits [87]. While the mechanisms behind these cognitive enhancements remain elusive, the effects appear primarily driven by improved metabolic health rather than direct effects on tau or amyloid pathology. In another study, voglibose, another AGI, demonstrated significant neuroprotective effects in a rat model of AD induced by intracerebroventricular streptozotocin (ICV-STZ) [88]. Voglibose treatment improved memory functions, attenuated acetylcholinesterase and malondialdehyde activity, enhanced antioxidant enzymes, reduced pro-inflammatory cytokines (TNF-α, IL-1β, CRP), and attenuated Aβ aggregation, highlighting its potential as a therapeutic approach for AD.

The exact mechanisms by which AGIs exert their neuroprotective effects remain to be fully elucidated, but several hypotheses have been proposed. AGIs may improve insulin sensitivity and glucose metabolism, potentially benefiting brain health and reducing the risk of AD. AGIs may contribute to improved glycemic control by inhibiting alpha-glucosidase and delaying glucose absorption, potentially lowering the risk of AD progression in individuals with T2DM. Furthermore, AGIs like miglitol and voglibose have shown an affinity towards LRP6 proteins, suggesting their potential in modulating the Wnt signaling pathway, which plays a role in neurogenesis, synaptic plasticity, and suppression of tau phosphorylation and neuroinflammation in AD [176].

While preclinical evidence is promising, human studies directly investigating the effects of AGIs on AD pathology and cognitive function are lacking. The Bayesian network meta-analysis indicated that AGIs are associated with a significantly higher risk of dementia and AD compared to SGLT2i and sulfonylureas [177]. The incident dementia risk was notably elevated in patients using AGIs, while metformin showed a similar risk to SGLT2i. Sensitivity analysis confirmed this increased dementia risk, specifically with AGIs. The study highlighted that antidiabetic drugs with high hypoglycemic risk, such as AGIs, are linked to a greater risk of dementia and AD, emphasizing the role of recurrent hypoglycemic events in this association.

While preclinical evidence has shown promising results for AGIs in managing AD, recent clinical findings raise concerns about their potential to increase the risk of dementia and AD, particularly in individuals experiencing recurrent hypoglycemic events. These findings underscore the critical need for further research to fully understand the long-term effects of AGIs on cognitive function and AD progression in both individuals with diabetes and those at risk of AD. Until more conclusive evidence is available, caution should be exercised when considering the use of AGIs in populations susceptible to AD or dementia. Future research should prioritize the development of safer and more effective AGIs, potentially derived from natural products such as mangiferin and quercetin, without the associated cognitive risks, offering promising therapeutic approaches to treat both T2DM and AD [178–180].

2.8. Sulfonylureas

Sulfonylureas are oral antidiabetic drugs often used as second-line adjunct medications in the treatment of T2DM. They act by closing the ATP-sensitive potassium channels in the pancreatic β-cell plasma membrane, ultimately resulting in the release of insulin [181]. These channels are also expressed in brain areas, including the hippocampus, frontal cortex, amygdala, and hypothalamus, playing an essential role in neuroprotection, synaptic transmission, neuroplasticity, and overall, in the pathogenesis of AD [182].

In animal studies, tolbutamide, when used in subclinical doses, restrained Aβ-induced memory deficit, hippocampal network activity inhibition, and reestablished long-term synaptic plasticity balance [89]. In rats with T2DM and sporadic AD, glibenclamide, a glyburide in the sulfonylurea class, was shown to improve memory impairment and reduce glucose and hippocampal inflammation [90]. Glibenclamide increased serum insulin levels while reducing serum inflammatory cytokines (TNF-α and IL-6) in the hippocampus of rats. Furthermore, glibenclamide administration in Aβ-treated rats decreased hippocampal hyperphosphorylated tau protein and improved learning and memory [91].

Clinical trials investigating the impact of sulfonylureas on AD and cognition are relatively lacking compared to the other antidiabetic drugs. In addition, cohort studies and existing evidence on the use of sulfonylureas in patients with T2DM and the risk for all-cause dementia and AD have yielded mixed results.

When comparing sulfonylurea users with non-users, some studies reported no association with cognitive performance, while others found that long-term sulfonylurea use did not alter the risk of developing AD [143,183,184]. However, several comparative cohort studies reported that metformin, DPP4i, or SGLT2i exhibited lower dementia risk than sulfonylureas [177,185,186]. Among the first-line antidiabetic treatments, metformin had the lowest risk of developing dementia, while SGLT2i showed the lowest risk of dementia compared to sulfonylureas as second-line agents [177]. The risk of AD was also substantially lower than sulfonylureas with metformin and SGLT2i [177]. In patients without diabetes complications, it was noted that sulfonylureas displayed significantly higher risks of dementia and AD over DPP4i and thiazolidinediones [177]. A population-based cohort study involving 37,030 new sulfonylurea users found that sulfonylureas were associated with a higher risk of dementia compared to new uses of DPP4 inhibitors in older adults with diabetes [185]. The intention-to-treat analysis showed a 9% higher dementia risk associated with sulfonylurea use, a finding that remained consistent across most sensitivity analyses. Furthermore, the as-treated analysis indicated a 15 % increased risk of dementia, suggesting that continuous sulfonylurea use may elevate the risk even with shorter exposure durations. The study also highlighted that glyburide showed a larger association with higher dementia risk than gliclazide. However, the observed E-value was small, suggesting that the estimate would not require a strong unmeasured confounder to generate the observed magnitude. While these findings suggest a potential link between sulfonylurea use and increased dementia risk, the authors warranted some caution in interpreting the results [185]. In a study comparing the effects of metformin and sulfonylureas on dementia risk in US patients over 50 with T2DM, it was found that metformin users had a lower risk of all-cause dementia, AD, and vascular dementia (VD) compared to sulfonylurea users [186]. These findings support the hypothesis that metformin may offer greater neuroprotection against dementia than sulfonylureas. Interestingly, combined treatment of metformin with sulfonylureas reduced the risk of dementia by 35 % over an 8-year period [139].

Given the potential risks, particularly hypoglycemia and other adverse effects, the American Geriatrics Society (AGS) Beers Criteria advises caution when prescribing sulfonylureas to older patients. The emergence of newer antidiabetic medications with improved safety profiles have made sulfonylureas less favored, especially in this population. Despite this, sulfonylureas remain commonly prescribed after metformin.

In conclusion, the relationship between sulfonylureas and AD remains a complex and evolving field of research. While animal studies suggest a potential neuroprotective role, human studies are less conclusive. More research and clinical trials are essential to clarify these findings and determine whether sulfonylureas hold any therapeutic promise for AD while considering potential adverse effects, such as hypoglycemia, in the vulnerable elderly population who have an increased risk of AD. The link between recurrent hypoglycemia and increased dementia risk underscores the importance of caution in this regard [177].

Until then, healthcare providers must carefully weigh sulfonylureas' potential benefits and risks, particularly for older individuals. Fortunately, the availability of newer antidiabetic drugs offers alternative treatment options with potentially fewer adverse effects, providing a hopeful outlook for the future of diabetes treatment and potential

reduction in dementia.

3. Challenges and opportunities

3.1. Challenges in translating preclinical findings to clinical practice

Translating preclinical findings to clinical practice is complex, with challenges arising from several key factors.

3.1.1. Species differences

While animal models, such as rodents, are valuable tools in preclinical studies, they may not fully replicate the intricate pathophysiology of AD in humans due to variations in brain structure, metabolism, and immune responses. This can lead to discrepancies in drug efficacy and safety profiles. As such, clinical trials involving antidiabetic drugs for patients with MCI and early AD are crucial for evaluating the translation of preclinical findings to real-world clinical practice.

3.1.2. Disease heterogeneity

AD is a multifaceted disease with various underlying causes and progression rates. Preclinical models often focus on a single aspect of the disease, making it challenging to predict a drug's performance in a diverse patient population.

3.1.3. Limited biomarkers

The lack of reliable biomarkers for early AD progression detection and monitoring complicates patient selection for clinical trials and drug efficacy assessment. However, recent advancements in biomarker research offer renewed hope, particularly in the reliability, specificity, and selectivity of AD biomarkers like Aβ and tau phosphorylation [187,188].

Despite these challenges, the ongoing clinical trials investigating the potential of antidiabetic drugs in MCI and early AD patients without diabetes (Table 2), combined with advancements in biomarker research [187,188], present a transformative approach to therapy investigation and renewed hope for successfully translating preclinical findings into effective clinical treatments.

3.2. Clinical trials involving antidiabetic drugs for MCI and early AD patients

Most evidence supporting the use of antidiabetic drugs for AD comes from observational studies in diabetic populations. These studies suggest a potential association between antidiabetic medication use and reduced dementia/AD risk or improved cognition. However, the question remains: Can these medications be effectively repurposed for MCI and early AD patients without diabetes? Well-designed clinical trials targeting this specific population are essential to address this question. Refining patient selection criteria based on genetic factors (e.g., APOE status), disease stage, and comorbidities could improve the success of these trials.

Such trials would evaluate the potential of these medications in a population without pre-existing diabetes and allow for a comprehensive evaluation of the risk-benefit profile in this context. It is essential to develop more refined and wide-ranging outcome measures that can capture improvements in cognitive and functional aspects and biomarker changes encapsulating Aβ pathology, tau phosphorylation, neuroinflammation, and immune response [188]. This is vital for determining the actual influence of antidiabetic drugs on AD progression and guide treatment strategies.

3.3. Brain-targeted formulations and personalized medicine approach (addressing hypoglycemia and adverse effects)

Older antidiabetic drugs, while promising in mitigating AD pathology, carry the risk of hypoglycemia, particularly in elderly patients. Future research could focus on developing formulations that bypass the blood-brain barrier and deliver drugs directly to the brain. This could enhance effectiveness and decrease systemic side effects, similar to the effects observed with intranasal insulin. As we expand our knowledge of AD biomarkers [187,188], identifying biomarkers that can predict individual responses to various antidiabetic drugs could lead to personalized treatment plans that optimize benefits and minimize risks.

3.4. Balancing benefits and risks

The decision to use antidiabetic drugs in AD patients requires careful evaluation of benefits and risks. While these drugs may offer potential cognitive benefits, their adverse effects can be a major concern, especially in elderly populations. Clinical trials in MCI and early AD patients would be instrumental in quantifying the benefits and risks associated with these drugs, allowing for informed decision-making regarding their use in this specific population. Table 2 presents a summary of ongoing clinical trials investigating the potential of antidiabetic drugs in individuals with MCI or early AD without diabetes.

3.5. Combination therapies

Given the multifactorial aspect of AD, combining antidiabetic drugs with other AD drugs targeting different disease aspects (e.g., Aβ-lowering therapies, tau-targeting drugs, anti-inflammatory) could enhance therapeutic efficacy. Evaluating the combination therapies in clinical trial will be crucial as we learn more about antidiabetic drugs and their role in mitigating AD in humans.

4. Discussion

The complex link between T2DM and AD underscores the potential for repurposing antidiabetic drugs as novel AD therapies. Both diseases share common pathophysiological features, such as impaired insulin signaling, chronic inflammation, and oxidative stress, which contribute to neurodegeneration and cognitive decline.

This study aimed to investigate the relationship between T2DM and AD, exploring the potential of antidiabetic drugs to treat neurodegeneration and reduce AD-associated pathology. Both AD and DM are prevalent diseases with overlapping pathophysiology. Patients with DM often experience cognitive decline due to the accumulation of Aβ plaques, tau proteins, and similar biochemical pathways.

Several antidiabetic drugs have shown promise in preclinical studies, demonstrating neuroprotective effects, reducing AD-associated neuropathology, and improving cognitive impairment. Notably, GLP-1 agonists are currently undergoing human trials for AD, with preclinical findings suggesting potential benefits in cognitive function and disease progression. Metformin, while showing promise in animal studies, has not consistently demonstrated a significant impact on AD biomarkers in human trials. Thiazolidinediones have produced mixed results, with some studies indicating cognitive improvement while others failed to show a delay in cognitive impairment.

DPP4i have effectively reduced amyloid burden and provided neuroprotective effects in preclinical AD studies. Human observational studies suggest they may reduce the risk of dementia, including AD, but further research is needed to confirm these findings. Intranasal insulin has shown potential in preclinical models, but clinical trials have yielded mixed results regarding its impact on cognitive function and AD biomarkers. SGLT2i, a new class of antidiabetic drugs, have shown promise in preclinical studies, and observational data suggests a potential association with a lower risk of dementia.

Among the older anti-diabetic drugs, AGIs have shown promise in preclinical AD models, potentially reducing Aβ aggregation and improving metabolic health. However, recent clinical findings raise concerns about an increased risk of dementia and AD, particularly with recurrent hypoglycemia. Similarly, sulfonylureas have shown mixed

Table 2
Ongoing clinical trials evaluating antidiabetic drugs in the MCI and/or early AD patients without diabetes.

Clinical trial ID	Study title	Phase	Study type	Subjects	Intervention	Primary end points	Relevant secondary endpoints
NCT05891496	A research study looking at the effect of semaglutide on the immune system and other biological processes in people with Alzheimer's disease	3	Interventional	Patients with MCI/AD Sex: All Age: 55–75	Semaglutide vs. placebo	Change in gene expression assessed by single-cell ribonucleic acid sequencing (scRNAseq) (cells in cerebrospinal fluid [CSF])	• Number of treatment-emergent adverse events (TEAEs). • Weekly average semaglutide concentration (Cavg) based on population pharmacokinetic (PK) analysis.
NCT04777396	A research study investigating semaglutide in people with early Alzheimer's disease (EVOKE)	3	Interventional	Patients with MCI/AD Sex: All Age: 55–85	Semaglutide vs. placebo	Change in the Clinical Dementia Rating — Sum of Boxes (CDR-SB) score	• Change in the Alzheimer's Disease Cooperative Study Activities of Daily Living Scale for MCI (ADCS-ADL-MCI). • Time to progression to dementia (CDR global greater than or equal to 1.0) among subjects with MCI (CDR global equal to 0.5) at baseline.
NCT04777409	A research study investigating semaglutide in people with early Alzheimer's disease (EVOKE plus)	3	Interventional	MCI or mild AD Sex: All Age: 55–85	Semaglutide vs. placebo	Change in the Clinical Dementia Rating — Sum of Boxes (CDR-SB) score	• Change in the Alzheimer's Disease Cooperative Study Activities of Daily Living Scale for MCI (ADCS-ADLMCI) score. • Time to progression to dementia (CDR global greater than or equal to 1.0) among subjects with MCI (CDR global equal to 0.5) at baseline. • Change in the 13-item Alzheimer's Disease Assessment Scale — Cognitive Subscale (ADAS-Cog-13) score.
NCT04098666	Metformin in Alzheimer's dementia prevention (MAP)	3	Interventional	Patients have reported subjective memory concerns, MMSE between ≥22 Sex: All Age: 55–90	Metformin vs. placebo	Free and Cued Selective Reminding Test (FCSRT)	• Alzheimer's Disease Cooperative Study Preclinical Alzheimer's Cognitive Composite (PACC-ADCS). • Cortical Thickness.
NCT05006599	SNIFF — 3 week Aptar CPS device	2	Interventional	Cognitively normal or MCI or mild AD Sex: All Age: 55–85	Insulin (Humulin® R U-100) vs. Placebo	Percentage of prescribed dose taken	• Change in the Preclinical Alzheimer Cognitive Composite 5 (PACC5) *Z*-Score. • Change in the 14-item Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog 14) Score. • Change in Aβ40 in Cerebrospinal Fluid (CSF).
NCT06391853	Investigating brain insulin resistance in Alzheimer's disease with intra-nasal insulin administration: a multimodal neuroimaging study	N/A	Interventional	Cognitively normal and/or patients with MCI/AD Sex: All Age: 21–85	Intranasal insulin vs. placebo	Effects of intranasal insulin on fMRI, PET-FDG, and EEG data	• Impact of intranasal insulin administration on cognition and episodic memory, spatial memory, and global memory performance. • Impact of intranasal insulin administration on attention/mental flexibility.
NCT05081219	SNIFF — Combo INI + EMPA trial	2	Interventional	Cognitively normal or MCI or mild AD	Intranasal insulin and	Number of participants with treatment-related	• Change in the Preclinical Alzheimer Cognitive

(*continued on next page*)

Table 2 (*continued*)

Clinical trial ID	Study title	Phase	Study type	Subjects	Intervention	Primary end points	Relevant secondary endpoints
				Sex: All Age: 55–85	empagliflozin vs. placebo	serious adverse events as assessed by CTCAE v5.0	Composite 5 (PACC5) Z-Score. • Change in the 14-item Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog 14) Score. • Change in Aβ40 in cerebrospinal fluid (CSF).
NCT06072963	Combination of intranasal insulin with oral semaglutide to improve cognition and cerebral blood flow: a feasibility study	2	Interventional	Diagnosis of MCI (based on a MOCA (Montreal Cognitive Assessment) <27 and a clinical dementia rating scale [CDR] score of 0.5 representing questionable dementia) Diagnosis of metabolic syndrome. Sex: All Age: 60–90	Intranasal insulin + semaglutide vs. placebo	Cognitive change: the effect of the combination of semaglutide and intranasal insulin on cognitive functioning. Neuroimaging outcome: The effect of the combination of semaglutide and intranasal insulin on cerebral blood flow (CBF).	• Change in specific cognitive domains: the effect of the combination of semaglutide and intranasal insulin on executive functions and episodic memory. • Neuroimaging outcomes: the effect of the combination of semaglutide and intranasal insulin on gray matter and hippocampal volume. • Functional outcome: the effect of the combination of semaglutide and intranasal insulin on functional performance.

results in AD research. While animal studies suggest potential neuroprotective effects, human studies are less conclusive, with some suggesting an increased risk of dementia compared to other antidiabetic medications.

One limitation of this literature review is that more data is from preclinical studies than human studies. Therefore, more randomized clinical trials and studies are necessary to support the current findings and see whether they translate to the human population.

5. Conclusion

Antidiabetic drugs, particularly GLP-1 RAs, DPP4i, and SGLT2i, represent a promising avenue for developing novel therapeutic approaches for AD. These drugs have demonstrated compelling preclinical evidence, with potential benefits in reducing Aβ plaques, tau tangles, neuroinflammation, and improving cognitive function. Observational clinical studies have also suggested potential cognitive benefits in individuals with T2DM. However, further research, particularly well-designed clinical trials with longer durations and larger sample sizes focusing on patients with MCI and early AD without diabetes, is crucial to validate their efficacy and safety in this specific population.

Developing reliable biomarkers to track disease progression and predict individual responses to treatment will be essential for personalized medicine approaches. Exploring combination therapies with other AD drugs and developing brain-targeted formulations could further enhance the therapeutic potential of these medications. By addressing these challenges and opportunities, we can accelerate the development of novel and effective treatment options for AD, leveraging the existing knowledge and therapeutic potential of antidiabetic drugs to potentially improve the lives of millions affected by this devastating disease.

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Jacky Tran: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation. **Sneh Parekh:** Writing – review & editing, Writing – original draft, Validation, Investigation, Formal analysis, Data curation. **Julia Rockcole:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation. **Danielle Wilson:** Writing – review & editing, Writing – original draft, Validation, Investigation, Formal analysis, Data curation. **Mayur S. Parmar:** Writing – review & editing, Visualization, Validation, Supervision, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Not applicable.

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