

DRUG REPURPOSING FOR ALZHEIMER'S DISEASE: CURRENT STRATEGIES, THERAPEUTIC POTENTIAL AND CLINICAL CHALLENGES

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Abstract

Alzheimer's disease represents a progressive neurological disorder distinguished by cognitive impairment and memory deterioration resulting from amyloid- β plaque accumulation and neurofibrillary tangle development within cerebral tissue. Pharmaceutical research endeavors targeting Alzheimer's disease have encountered significant obstacles due to predominantly failed clinical trials over the preceding ten years. Drug repurposing, defined as identifying novel therapeutic applications for existing medications or pharmaceutical compounds, constitutes a viable and opportune approach to drug development, especially concerning Alzheimer's disease. Methodologies and tactics are formulated according to AD pathophysiology, encompassing amyloid-related pathology, tau-associated pathology, oxidative damage, mitochondrial impairment, neuroinflammatory processes, and autophagic mechanisms. Pharmaceutical repurposing methodologies encompass computational approaches including molecular docking studies, alongside experimental investigations utilizing rodent models. According to substantial supporting evidence, high-priority repurposed therapeutic agents can be categorized into antimicrobials, antihypertensive medications, antidiabetic compounds, antidepressant drugs, among others. This review examines the diverse pathophysiological mechanisms of AD, methodological approaches, and comprehensive details regarding repurposed medications. Additionally, it addresses obstacles and prospective directions for drug repurposing in AD research.

Keywords: Alzheimer's disease, Drug repurposing, Amyloid pathology, Tau pathology and Computational techniques.

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INTRODUCTION

Alzheimer's disease (AD), designated in honor of the German psychiatrist Alois Alzheimer, represents the predominant form of dementia [1]. This condition manifests as a gradually advancing neurodegenerative disorder distinguished by the presence of neuritic plaques and neurofibrillary tangles resulting from amyloid-beta peptide ($A\beta$) deposition primarily within the medial temporal lobe and neocortical regions of the brain [1, 2]. Upon examining the brain tissue of his initial patient, who had experienced memory impairment and behavioral alterations prior to death, Alzheimer identified amyloid deposits and substantial neuronal loss, leading him to characterize this condition as a severe cerebral cortical pathology. The deterioration of cognitive abilities may arise from neurological conditions such as Alzheimer's disease

(AD) or alternative etiologies including toxic exposure, infectious processes cardiovascular and respiratory dysfunction that compromises cerebral oxygenation, malnutrition, vitamin B12 insufficiency, neoplasms, and various other causes [3].

The incidence of Alzheimer's disease (AD) is progressively rising. The worldwide population affected by Alzheimer's disease is projected to increase from 57 million to 153 million by 2050 [4]. The authorization of anti-amyloid monoclonal antibodies constitutes notable advancement in Alzheimer's disease therapeutics, though its application is restricted to early disease phases and depends on diagnostic and treatment technologies with limited accessibility.

Repurposing constitutes an effective pharmaceutical development approach that can accelerate novel therapeutic advancement more rapidly and

economically compared to developing NMEs. Contemporary computational approaches, laboratory and animal studies, pharmacoepidemiological analyses, and clinical observations can all contribute to generating candidate selection evidence [5].

Drug repurposing, alternatively termed drug repositioning, reprofiling, or re-tasking, involves discovering new therapeutic applications for approved or investigational compounds beyond their initial medical indication. This strategy offers numerous benefits compared to developing entirely novel medications for specific indications [6]. Primarily, the probability of failure is diminished; when early-phase studies have demonstrated adequate safety of the repurposed compound in preclinical models and human subjects, it is less prone to failure, particularly regarding safety concerns, in subsequent efficacy studies. Additionally, the pharmaceutical development timeline can be shortened since most preclinical evaluation safety characterization, and in some instances, formulation optimization will have been previously completed. Furthermore, reduced financial investment is necessary, though this may differ considerably based on the developmental stage and approach of the repurposing candidate [6,7]. Traditionally, drug repurposing has been serendipitous and opportunistic. When a pharmaceutical compound was found to possess off-target or newly identified on-target effects, it was pursued for commercial development [8].

PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE

Alzheimer's disease represents a progressive neurodegenerative condition that systematically compromises cognitive functions including learning capacity, memory retention, and executive decision-making processes throughout the aging process. The cholinergic network, constituting a fundamental neurological system, facilitates optimal hippocampal functioning—the cerebral region responsible for memory consolidation. Within Alzheimer's pathophysiology, neurons utilizing acetylcholine, a neurotransmitter crucial for cognitive processes and memory formation, undergo progressive deterioration. Concurrently, specific neural receptors exhibit excessive activity, thereby exacerbating systemic imbalance. This process culminates in substantial acetylcholine depletion, most notably within the nucleus basalis of Meynert, which typically facilitates essential communication pathways to the hippocampus and cerebral cortex. The absence of these neural communications precipitates the decline of memory and cognitive capabilities. Research demonstrates that acetylcholine-synthesizing enzymes exhibit diminished activity, receptor availability for signal reception decreases, and acetylcholine release becomes compromised in Alzheimer's-affected brains. In contrast, acetylcholinesterase (AChE), the enzyme facilitating acetylcholine degradation, demonstrates

heightened activity. Consequently, acetylcholine undergoes accelerated depletion, compromising interneuronal communication and resulting in the characteristic cognitive disorientation and memory impairment observed in Alzheimer's disease [9].

The pathophysiological mechanisms underlying Alzheimer's disease initiate with extracellular amyloid- β 42 ($A\beta$ 42) plaque accumulation and Tau protein hyperphosphorylation,

subsequently generating intracellular neurofibrillary tangles (NFTs). These processes trigger oxidative stress, compromise mitochondrial function, promote neuroinflammation, induce excitotoxicity, and disrupt insulin signaling pathways, collectively culminating in neuronal apoptosis.

myloid- β ($A\beta$) Accumulation:

In the context of Alzheimer's disease, the β -site APP cleaving enzyme 1 (BACE 1), alternatively termed β -secretase, processes the amyloid precursor protein (APP). Subsequently, γ -secretase acts upon the membrane-associated C99 fragment, comprising 99 amino acids, generating diverse $A\beta$ peptides. The predominant species include the 40-amino acid ($A\beta$ 1-40) and 42-amino acid ($A\beta$ 1-42) isoforms [9]. While both exhibit neurotoxic properties, the latter demonstrates enhanced propensity for aberrant folding and deleterious aggregation, thereby contributing to AD pathophysiology. Additionally, these aggregates undergo extracellular deposition, triggering a series of pathological modifications including synaptic network impairment and neuronal demise [10].

Laboratory studies have established a correlation between amylase's glycogen-metabolizing capacity and $A\beta$ 1-42 in human fetal primary astrocytes. This phenomenon was particularly evident upon exposure to fibrillar $A\beta$ 1-42. Fibrillar $A\beta$ 1-42 appears to influence amylase post-translational modifications rather than transcriptional regulation. Astrocytes positioned adjacent to $A\beta$ 1-42 deposits exhibit elevated pancreatic amylase immunoreactivity. The association between amylase and $A\beta$ 1-42 aggregates may stem from its capacity to establish protein complexes, beyond its glycogen-degrading function [11]. Research indicates that amylase functions as a protein carrier, transporter, modulator, and guardian of protein interactions. Utilizing an in vivo AD model to confirm colocalization between these entities and characterize potential interactions would prove valuable [10].

Tau Hyperphosphorylation and Neurofibrillary Tangle Development:

In physiological states, tau protein enhances tubulin assembly stability, thereby promoting microtubule structural integrity. During Alzheimer's disease pathogenesis, elevated $A\beta$ 42 fragment concentrations within the brain trigger excessive phosphorylation of microtubule-associated tau proteins. This hyperphosphorylated tau loses its capacity to establish stable associations with tubulin, consequently forming insoluble misfolded protein aggregates termed NFTs

[11]. These NFTs compromise physiological tau functionality, disrupt microtubule dynamic regulation mediated by tau, and contribute to neurodegeneration. The accumulation of NFT proteins within cerebral tissue results in neuronal and synaptic deterioration. Studies demonstrate a substantial correlation between A β deposition and NFT formation throughout neuroinflammatory and neurodegenerative processes in Alzheimer's disease [12].

NEUROINFLAMMATORY PROCESSES

Neuroinflammation represents a pathological sequence characterized by microglial and astrocytic activation, contributing significantly to AD pathophysiology. Persistent cerebral inflammation accelerates neuronal deterioration and disease advancement through the production of pro-inflammatory cytokines, reactive oxygen species, and additional neurotoxic compounds [2].

Oxidative Stress and Mitochondrial Impairment

In AD pathology, A β 42 plaques and NFTs activate microglia and astrocytes, resulting in ROS generation and inflammatory cytokine release. This process induces oxidative stress and neuroinflammation. ROS target proteins, lipids, and nucleic acids, causing oxidative damage that accelerates disease advancement. Additionally, ROS trigger neuronal apoptosis through mitochondrial pathways by upregulating pro-apoptotic proteins such as Bax while downregulating anti-apoptotic proteins like Bcl-2.

Mitochondrial A β 42 accumulation compromises respiratory complexes II and IV function, reduces cellular energy availability, enhances ROS generation, and facilitates cytochrome c release, ultimately activating caspase-3 and inducing apoptosis. NADPH oxidase, specifically the NOX2 isoform, contributes significantly to ROS generation by activating cytosolic components and enhancing superoxide anion production [13, 14]. During oxidative stress conditions, the transcription factor Nrf2 dissociates from Keap-1 and migrates to the nucleus, upregulating antioxidant enzymes including HO-1, SOD, GPx, and GST, thereby strengthening cellular defense mechanisms while reducing NOX2 activity and ROS generation. Nrf2 enhances neuronal viability through BDNF upregulation and facilitates A β 42 and p-Tau clearance via autophagy mechanisms.

SIRT1, functioning as an NAD⁺-dependent deacetylase, provides neuroprotection by mitigating oxidative stress, apoptosis, and inflammation while enhancing non-amyloidogenic APP processing. This enzyme facilitates Nrf2 function, suppresses pro-apoptotic genes such as P53 and Bax, elevates BDNF expression, modulates neuroinflammation through NF- κ B downregulation, and diminishes astrocytic reactivity by reducing GFAP expression.

Insulin signaling impairment

Suppression of insulin/IGF-I signaling through the PI3K-Akt pathway results in glycogen synthase kinase-3 β (GSK-3 β) activation, thereby promoting tau

phosphorylation and A β deposition [13]. Mitochondrial impairment, oxidative damage, and neuroinflammatory processes contribute to neuronal deterioration through both direct mechanisms and indirect pathways involving the exacerbation of insulin and IGF-I receptor insensitivity, consequently reducing PI3K-Akt signaling activity. Neurodegeneration further compromises cellular viability, neurogenesis, synaptic formation, preservation, and adaptability, along with metabolic processes. Beyond these detrimental neuronal consequences, disrupted insulin/IGF signaling pathways contribute to glial and cerebrovascular pathology in AD. The inhibition of PI3K-Akt and mTOR signaling pathways leads to oligodendrocyte impairment, compromising myelin preservation and structural stability, ultimately causing white matter atrophy and deterioration.

Further contributing factors encompass inflammatory and injurious conditions within astrocytes and microglia, alongside compromised endothelial and glial-vascular functions essential for maintaining BBB stability. Microvascular dysfunction in Alzheimer's disease may occur in association with or independently from A β pathology. Considering the established importance of functional insulin signaling in maintaining microvascular stability, the neuro-and glial vascular unit, and BBB function, the prevalence of microvascular abnormalities in AD is anticipated. The lack of recognition of this aspect as a core and intrinsic feature of AD has led to inadequate classification of study participants who exhibit non-A β microvascular pathology without concurrent A β vascular pathology [15].

Autophagy

Numerous research findings indicate that dysregulated autophagy processes contribute to various human pathological conditions, including Alzheimer's disease. In 2005, two studies employing immunogold labeling and electron microscopy demonstrated increased accumulation of autophagic vacuoles (AVs) in both human and APP/PS1 AD mouse brain tissue compared to age-matched control specimens, establishing the initial direct confirmation of compromised autophagy in AD. Reduced autophagic activity was similarly observed in Alzheimer's patient brain tissue and in APP-based animal, cellular, and *Drosophila* experimental models [9]. Compromised autophagy function (including Atg7 and ATG5 knockout) produces AD-like phenotypes in animal models, encompassing abnormal behavioral patterns, cognitive deficits, microglial activation, enhanced tau phosphorylation, A β deposition, and inflammasome stimulation.

The BECN1 gene, essential for autophagic processes, exhibits reduced expression in

Alzheimer's disease brain tissue. Research has demonstrated that BECN1 facilitates lysosomal breakdown of cell surface APP while reducing APP metabolite generation. NRBF2, a component of the BECN1 complex family, is similarly decreased in AD

human brain samples. AAV-mediated NRBF2 upregulation improves cognitive function and reduces A β deposition in AD animal models through autophagy pathway stimulation. Studies in AD mice reveal that compromised autophagy results in enhanced accumulation of autophagy adaptor protein 52 (NDP52) and p62, which commonly colocalizes with tau and A β [16].

Conversely, chronic exposure to accumulating pathogenic proteins can compromise autophagy and mitophagy mechanisms, worsening Alzheimer's disease pathophysiology. In the PDAPP20 Alzheimer's disease mouse model, microglial cells displaying autophagy receptor p62, ubiquitin, and Iba1 demonstrate resistance to A β accumulation. Increased p62 levels are typically considered indicators of defective autophagic function. Extended exposure resulting in A β peptide aggregation over 24-hour periods causes lysosomal dysfunction and elevates proinflammatory cytokine release in BV2 cells. This suggests a reinforcing cycle between compromised autophagy and toxic protein accumulation in Alzheimer's disease.

Autophagy enhancement may represent a therapeutic approach for eliminating detrimental substances in AD [17].

APPROACHES OR STRATEGIES TO DRUG REPURPOSING IN AD

Numerous pharmaceutical organizations are concentrating predominantly on drug repurposing/repositioning approaches because of the elevated failure rates and increased expenses linked to conventional drug discovery and development processes. The fundamental objective of these investigations is to identify novel therapeutic agents capable of modifying multiple molecular targets and controlling the degenerative pathological processes in AD.

Drug repurposing may prove highly beneficial for creating innovative medications substantially more rapidly and economically compared to traditional drug discovery methodologies [18].

Target based drug approaches

Target-oriented methodologies conventionally encompass three sequential phases: i) construction of the target's molecular framework; ii) preparation and conformational exploration of the ligands; and iii) evaluation through scoring systems that reflect the binding affinity of the ligand-target interaction. In target-oriented drug repositioning, proteins or biomarkers of significance involve high-throughput and/or high-content screening (HTS/HCS) of pharmaceutical compounds, subsequently followed by computational screening of compounds from pharmaceutical libraries, including ligand-oriented screening or molecular docking [19]. The target-oriented methodology presents benefits as it enables screening of virtually all therapeutic compounds possessing established chemical configurations. Nevertheless, target-oriented approaches demonstrate

constraints in identifying novel mechanisms beyond recognized targets. The NLRP3 inflammasome and the processes that trigger and promote its activity contribute to Alzheimer's disease pathogenesis and inflammatory responses. NLRP3 antagonists function through multiple mechanisms to diminish NLRP3 activation and inflammation. These compounds include MCC950 and OLT1177 (Dapansutrile), which reduce ATPase function necessary for NLRP3 activation, while JC124 prevents caspase-1 activation, IL-1 β release, and ASC clustering. VX-765 (Belnacasan) inhibits the activation of caspase 1 and 4 [20].

Network based drug repurposing: Network-based and pathway-oriented methodologies have been extensively utilized to identify pharmaceuticals or therapeutic targets suitable for repurposing applications. The construction of drug or disease networks utilizing gene expression profiles, pathological mechanisms, protein-protein interactions, or genome-wide association study information represents a systematic approach to network analysis that facilitates the identification of promising repurposing candidates [6]. Such networks enable the recognition of potential pharmaceutical agents for Alzheimer's disease through the modulation of critical pathways implicated in the pathogenesis. This approach not only accelerates the drug discovery pipeline but also mitigates associated risks and financial burdens. Investigators can optimize timelines by proceeding directly to phase II clinical investigations using previously approved therapeutic agents. Multiple promising compounds have been characterized and prioritized for clinical evaluation in Alzheimer's disease populations [8].

For instance, compelling research within metallodrug studies examines an anticancer cisplatin analogue functioning as a regulator of amyloid aggregation processes. Nevertheless, similar to network medicine approaches, the expanding data repository underscores the requirement for more advanced analytical instruments to completely harness drug-protein network capabilities. Brexpiprazole serves as supplementary therapy for treating major depressive disorder in adult populations and pediatric schizophrenia, and has been successfully repositioned as an authorized intervention for Alzheimer's disease-related agitation [5]. Semaglutide represents a glucagon-like protein-1 (GLP-1) receptor agonist sanctioned for diabetes and obesity management. Presently, it undergoes clinical investigation as a potential early Alzheimer's disease therapeutic. These two compounds constitute proprietary patented pharmaceuticals undergoing repurposing within commercial development pipelines. More frequently encountered are medications including rasagiline or rotigotine, originally authorized for Parkinson's disease management and subsequently explored through repurposing initiatives for AD following generic status acquisition.

Transcriptomics based approaches

Transcriptional profiling serves as a quantitative methodology for evaluating biological conditions associated with pharmacological responses to therapeutic agents or particular pathological states. This approach draws from "connectivity map" investigations, which originally established a repository of transcriptional profiles corresponding to various reference compounds [21, 22]. The fundamental objective of transcription-based pharmaceutical discovery focuses not on target identification but rather on recognizing therapeutic agents possessing disease-modifying characteristics through their comprehensive transcriptional effects. A particularly attractive aspect of this methodology is its natural applicability to drug repositioning of existing pharmaceuticals, circumventing the obstacles that novel compounds encounter during clinical development [23]. AD has undergone extensive examination regarding transcriptional modifications that accompany clinical and cognitive deterioration. The substantial body of evidence demonstrates consistent and identifiable alterations associated with this disorder, enhancing the attractiveness of a repositioning approach. Consequently, utilizing single-cell transcriptomic analysis to discover AD-related risk genes for therapeutic target identification may prove more efficacious, as it focuses on the principal cell-type-specific genes implicated in AD pathogenesis. Alsterpaullone possesses multiple targets and can intervene during both presymptomatic and disease advancement phases. Its favorable toxicity profile supports clinical trial feasibility [24]. Chrysin demonstrates remarkably few side effects and is currently under investigation for inflammatory and neurological conditions. This compound's anti-inflammatory characteristics and symptomatic benefits render it appropriate for redesign and repurposing initiatives [25].

Computational molecular docking

Molecular docking represents a structure-dependent computational methodology for forecasting the binding compatibility between ligands (including pharmaceutical compounds) and targets (including receptors). When a disease-associated receptor target has been identified, multiple pharmaceutical agents can be evaluated against it through conventional docking procedures involving a single target with various ligands [6]. Acetylcholinesterase serves as a protein target for Alzheimer's disease-related ligands, with its mechanism being exemplified by therapeutic agents such as Huperzine. This methodology enables the assessment of ligand binding efficacy to acetylcholinesterase protein, which plays a crucial role in Alzheimer's disease therapeutic interventions [26]. High-throughput ligand-protein reverse docking exemplifies another docking-based repurposing strategy, as demonstrated in the identification of potential Alzheimer's therapeutics through their strong binding interactions with seven AD-associated target proteins,

including compounds like droperidol [27]. Through extensive virtual screening of 1553 FDA-sanctioned medications, researchers employed docking simulations to evaluate binding free energy calculations for each

pharmaceutical compound against seven AD target proteins. A notable limitation of docking-based methodologies, similar to other structure-dependent approaches, involves the necessity for X-ray crystallographic structures or NMR data of both pharmaceutical compounds and their targets [28].

Polypharmacology based drug repurposing

Polypharmacology encompasses the development or utilization of therapeutic compounds that interact with multiple molecular targets. These pharmaceutical interventions may consist of combination therapies involving several distinct medications that bind to different targets, or alternatively, individual compounds that engage with multiple targets, termed multitarget ligands (i.e., multi-target-directed ligands) [29]. Combination approaches offer enhanced adaptability and individualized treatment options relative to monotherapeutic strategies.

Individual molecules present potential benefits including (i) unified pharmacokinetic properties that facilitate concurrent modulation of multiple cerebral targets; (ii) enhanced safety profiles through reduced potential for drug-drug interactions; and (iii) improved patient adherence via streamlined treatment protocols [30].

The unsuccessful outcomes of highly selective and potent therapeutic agents during clinical trials, along with the restricted treatment effectiveness of mono-target pharmaceuticals, are promoting the advancement of multi-target compounds. Beyond the achievements observed in combination treatment approaches, employing a single therapeutic agent that influences multiple targets may offer clinical advantages. Research has demonstrated that the combination of cromolyn and ibuprofen decreases A β aggregation concentrations and promotes the anti-inflammatory M2 phenotype, which enhances A β phagocytosis in the Tg2576 AD mouse model [31].

THERAPEUTIC POTENTIAL OF DRUG REPURPOSING IN AD:

Anti-inflammatory medications:

Cyclooxygenase-1 and cyclooxygenase-2 represent enzymes that generate prostaglandins (PGEs), resulting in neuroinflammatory processes and synaptic dysfunction within the central nervous system. The peroxidase function of cyclooxygenase contributes to reactive oxygen species formation throughout prostaglandin synthesis. Additionally, PGE1 and PGE2 enhance glutamate discharge from astrocytic cells, leading to excitotoxic damage. Valeryl salicylate, functioning as a specific COX-1 antagonist, and etoricoxib, serving as a targeted COX-2 antagonist, demonstrated potential for enhancing cognitive function in streptozotocin (STZ)- treated rodents.

These compounds prevented STZ-mediated acetylcholinesterase stimulation and oxidative damage [32]. Conversely, phenacetin, a specific COX-3 antagonist, failed to demonstrate neuroprotective effects.

Salicylate demonstrated efficacy in ameliorating cognitive decline and synaptic dysfunction induced by A β 42 in rodent models, while also providing protection against tau-related pathology in PS19 transgenic mice representing frontotemporal dementia. Additionally, celecoxib, a targeted COX-2 antagonist, exhibited enhanced memory function and neurogenesis in aluminum chloride (AlCl₃)-treated rats. This compound reduced AlCl₃-induced acetylcholinesterase stimulation, astroglial activation, and programmed cell death. Celecoxib further demonstrated anti-neuroinflammatory and neuroprotective properties against A β 42 accumulation and excitotoxic injury in lipopolysaccharide (LPS)-administered mice [9].

Cysteinyl leukotrienes (CysLTs)

Cysteinyl leukotrienes (CysLTs) have been recognized as a principal inflammatory lipid mediator in Alzheimer's disease (AD). The central nervous system possesses the capacity to synthesize CysLTs, predominantly via transcellular mechanisms within neurons and glial cells. This transcellular synthesis of CysLTs influences central nervous system neuronal cell functionality through CysLT receptor pathways. Human brain tissue exhibits lower CysLT1 receptor expression compared to CysLT2 receptors. Throughout persistent neuroinflammation and the aging process associated with Alzheimer's disease, both CysLT1 and CysLT2 receptor expression increases in astrocytes, microglial cells, and cells with neuronal and glial characteristics [11]. Montelukast, a commercially available CysLT1 receptor antagonist utilized for asthma treatment, is presently being evaluated in phase II clinical trials for Alzheimer's disease. Preclinical investigations revealed that montelukast enhanced hippocampal neurogenesis, diminished neuroinflammation, and ameliorated learning and memory functions in experimental models of brain aging and mild cognitive impairment [33].

JAK inhibitor Baricitinib, which functions as a JAK inhibitor for rheumatoid arthritis treatment, demonstrated enhancement of memory function in d-galactose (d-gal)/ovariectomy (OVX) rodent models. Within these d-gal/OVX subjects, the compound suppressed JAK2/STAT3 and PI3K/AKT/mTOR signaling cascades, thereby providing neural protection against A β 42 accumulation, oxidative damage, inflammatory responses in neural tissue, and astrocytic activation [9].

Anti-hypertensive medications

Elevated blood pressure during midlife increases the likelihood of developing Alzheimer's disease in subsequent years. Antihypertensive medications including angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers (CCBs), and angiotensin-I receptor

blockers (ARBs) have undergone evaluation as prospective AD therapeutic interventions. Several of these pharmaceutical agents exhibited anti-amyloid properties in cellular cultures and murine Alzheimer's disease models [18, 34].

Angiotensin converting enzyme inhibitors

Laboratory investigations reveal that ACE facilitates the degradation of amyloid peptides (A β -40 and A β -42), whereas ACE inhibitors captopril and lisinopril impede this process. These ACE inhibitors represent frequently prescribed antihypertensive medications. Additional investigation is required to establish whether ACE pharmaceutical agents can elevate A β concentrations in living systems. Captopril failed to demonstrate A β accumulation in elderly APP transgenic mice [9]. Moreover, brain-penetrant ACE inhibitors including captopril and perindopril not only reduce Alzheimer's disease occurrence in elderly hypertensive individuals, but also decelerate cognitive decline in patients with mild to moderate Alzheimer's disease [18, 35].

Angiotensin Receptor Blockers

Telmisartan functions as an AT1 receptor antagonist that enhanced cognitive function in rats administered AlCl₃. This compound reduced AlCl₃-mediated A β ₄₂ accumulation, tau protein aggregation, AchE stimulation, neuroinflammatory responses, and oxidative injury. Telmisartan additionally attenuated inflammatory processes in A β 42-treated animals. Moreover, candesartan, another AT1 receptor antagonist, has demonstrated efficacy in diminishing STZ-mediated AchE stimulation and oxidative stress in murine models [9, 34].

Calcium Channel Blockers

Nilvadipine represents a dihydropyridine-class CCB with blood-brain barrier permeability. In experimental Alzheimer's disease models, nilvadipine treatment enhanced cognitive performance and memory function through reduction of cerebral A β concentrations and facilitation of its clearance [7, 34]. Diltiazem, a benzothiazepine-based non-dihydropyridine Ca⁺² channel antagonist, demonstrated capacity to reverse STZ-mediated cognitive deficits in rodents. This agent diminished STZ-induced A β 42 deposition, neuroinflammatory cascades, and oxidative injury. Additionally, diltiazem has exhibited inhibitory effects on AchE stimulation and oxidative stress in AlCl₃-treated mice [9].

Inhibitors of the phosphodiesterase-5 (PDE-5) enzyme

Research has examined the role of the phosphodiesterase-5 (PDE-5) enzyme in controlling cyclic guanosine monophosphate (cGMP) and its connection to Alzheimer's disease. Elevated cGMP concentrations activate cerebral intracellular protein kinase, resulting in neuroplasticity, excessive tau phosphorylation, and A β accumulation [9, 19]. Recent studies have explored sildenafil and tadalafil (PDE-5 inhibitors utilized for erectile dysfunction treatment) in both preclinical and clinical Alzheimer's disease

models. Sildenafil demonstrates effective suppression of neuroinflammation and A β accumulation in aging murine models [36]. Tadalafil exhibited superior performance compared to sildenafil regarding effectiveness, neuroprotective properties, and cognitive enhancement, attributed to its enhanced ability to inhibit the PDE-5 enzyme through improved blood-brain barrier permeability [36, 37].

ANTIDIABETIC MEDICATIONS

GLP-1 receptor agonists: GLP-1 represents an endogenous peptide hormone predominantly secreted by intestinal L-cells following nutrient consumption, functioning to enhance insulin release while demonstrating neuroprotective characteristics within the central nervous system. This hormone facilitates glucose-dependent insulin secretion and synthesis, supports optimal insulin signaling pathways, maintains glycemic homeostasis, inhibits glucagon release, delays gastric emptying, and diminishes appetite [4]. GLP-1-based therapeutics, encompassing compounds such as exenatide and liraglutide, constitute antidiabetic agents that enhance insulin secretion. Multiple research investigations have indicated that these peptides possess potential as neuroprotective compounds in AD. Preclinical research has established that these agents can attenuate pathological processes associated with Alzheimer's disease, encompassing A β plaque accumulation, microglial activation, and cognitive enhancement. Biguanide compounds, particularly metformin, represent oral antihyperglycemic agents that have undergone investigation for AD therapy due to their neuroprotective characteristics, including attenuation of etoposide-induced neuronal apoptosis and enhancement of oxygen-glucose availability during neuronal injury via various autophagy-related pathways. Metformin demonstrated substantial dementia risk reduction in individuals aged 50 years and above compared to untreated control groups [15, 34].

PPAR- γ agonists stimulate central PPAR- γ receptors, thereby diminishing A β 42 accumulation, neuroinflammation, and glutamate-induced excitotoxicity through enhanced GLT-1 expression. This mechanism results in improved glutamate clearance and reduced excitotoxic damage. These compounds address neurodegeneration via diverse pathways beyond PPAR γ receptor modulation. Clinical trials examining rosiglitazone and pioglitazone demonstrated favorable outcomes exclusively for pioglitazone in individuals with mild to moderate Alzheimer's disease [11, 15].

Sulfonylurea medications, encompassing glyburide and glipizide, inhibit mTOR signaling.

Glyburide functions through inflammasome suppression, reducing excessive proinflammatory cytokine production that contributes to neuroinflammation associated with Alzheimer's disease [13]. Intranasal insulin administration represents a

targeted therapeutic approach that enhances cognitive function and biomarker profiles, including glucose utilization, CSF A β , and tau protein concentrations [4, 15].

Given that DPP-4 functions as a negative modulator of incretins, inhibitors targeting DPP-4

have the potential to enhance incretin activity within the central nervous system and provide protection against neurodegeneration, similar to observations with GLP-1RA medications [4]. The DPP-4 inhibitors currently employed in therapeutic settings encompass sitagliptin, vildagliptin, saxagliptin, alogliptin, and linagliptin, which may be administered as monotherapy or combined with metformin. In experimental AD rodent studies, linagliptin, a BBB- penetrating DPP-4i, demonstrated elevation of GLP-1 levels while reducing hippocampal A β accumulation, IRS-1 serine phosphorylation (S307), GSK-3 β enzymatic activity, TNF- α , IL-1 β , IL-6, acetylcholinesterase expression, and oxidative/nitrosative damage [9, 15].

SGLT2 inhibitors similarly exhibit neuroprotective characteristics and represent potential therapeutic agents for addressing Alzheimer's disease or cognitive decline associated with T2DM. Canagliflozin, an SGLT-2 antagonist utilized in T2DM management, has demonstrated enhancement of cognitive performance and neuronal maturation. Additionally, this compound attenuates A β 42 accumulation, Tau protein aggregation, AchE enzymatic activity, neuroinflammatory responses, and oxidative damage [9, 15].

ANTICANCER THERAPEUTICS

AstraZeneca developed Saracatinib (designated AZD0530) as an oncological therapeutic agent. This compound functions as an orally administered inhibitor of SRC tyrosine kinase family proteins, which modulate malignant cell adherence, motility, and invasiveness. While demonstrating acceptable clinical tolerability, phase II investigations revealed limited efficacy when employed as monotherapy for cancer treatment, leading to its deprioritization. Nevertheless, with advancing knowledge regarding SRC kinase involvement across various pathological conditions, multiple research initiatives have emerged exploring saracatinib's

therapeutic repurposing potential [6]. Additionally, laboratory investigations have established that compounds including nilotinib, neratinib, axitinib, binimetinib, sunitinib, ibrutinib, abemaciclib, and regorafenib demonstrate capacity to ameliorate cognitive deficits [9]. Thalidomide represents an oncological agent currently undergoing phase III clinical evaluation, which has been shown to modulate BACE-1 activity while suppressing endothelial cellular proliferation and neovascularization processes, additionally compromising blood-brain barrier integrity. TNF α antagonists demonstrate potential for reducing hippocampal neuronal degeneration. Carmustine, characterized as a non-ionizing

nitrosoare compound functioning as an alkylating therapeutic in cerebral malignancies, has exhibited capacity to suppress A β generation and enhance tau-related pathology in preclinical studies when administered at non-cytotoxic concentrations [11].

ANTIDEPRESSANT MEDICATIONS

Antidepressant compounds are categorized into several groups including monoamine oxidase inhibitors, tricyclic compounds, SSRIs, and serotonin norepinephrine reuptake inhibitors. Multiple pharmaceutical agents within each antidepressant category have exhibited neurogenesis promotion in animal studies through varied mechanistic pathways. As an illustration, brexpiprazole, functioning as a serotonin/dopamine activity modulator, has undergone numerous clinical investigations for managing agitation in Alzheimer's disease based on encouraging findings from earlier studies. The serotonin reuptake inhibitor escitalopram has undergone evaluation for agitation management. The tricyclic compound amitriptyline demonstrated reduction in A β 42 accumulation and enhancement of neurogenesis in APP/PS1 transgenic mouse models [9,18,34].

ANTIMICROBIAL AGENTS

Contemporary research reveals an association between gut microbiome dysbiosis and Alzheimer's disease development. With accumulating evidence regarding the gut-brain axis relationship, researchers are investigating antimicrobial therapy as a potential intervention for Alzheimer's disease. Nevertheless, only specific antimicrobial categories have demonstrated promise in reducing neuroinflammation linked to microbiome imbalance, potentially providing therapeutic advantages for Alzheimer's patients. Certain antimicrobials including rifampicin, minocycline, and rapamycin have been shown in animal research to diminish cerebral A β concentrations [11,34]. These compounds additionally appear to suppress inflammatory mediators and stimulate microglial cells, which participate in infection defense mechanisms. Although these antimicrobials have demonstrated anti-inflammatory properties and enhanced cognitive function in Alzheimer's animal models, their therapeutic efficacy in human subjects remains undetermined.

ADDITIONAL COMPOUNDS

Lithium, a mood-regulating agent frequently employed in psychiatric conditions including bipolar disorder, has emerged as a promising candidate for drug repositioning in Alzheimer's disease treatment. Through its inhibitory action on glycogen synthase kinase 3 β (GSK3 β), lithium presents therapeutic potential in Alzheimer's disease, given that GSK3 β plays a role in excessive tau phosphorylation. Clinical investigations have demonstrated lithium's capacity to benefit Alzheimer's patients through the deceleration of cognitive deterioration [2, 38]. Sodium benzoate

represents another potential repurposing candidate for AD, serving as both a cinnamon metabolite and an FDA-approved preservative utilized in managing urea cycle disorders [2]. Levetiracetam, an antiepileptic agent that modifies synaptic vesicle glycoprotein 2A activity, is employed to address neuronal hyperexcitability characteristic of Alzheimer's disease. Research has demonstrated levetiracetam's ability to suppress subclinical hippocampal seizures and electrical spikes through foramen ovale electrode monitoring in Alzheimer's cases, suggesting effectiveness in reducing hippocampal hyperexcitability that contributes to AD pathological processes [9, 18, 39].

CHALLENGES IN DRUG REPURPOSING OF AD

Pharmaceutical repurposing represents a particularly attractive approach for rare diseases due to both scientific and economic considerations. From a scientific perspective, these conditions often exhibit limited pathophysiological understanding, with insufficient knowledge concerning the molecular pathways underlying disease progression [6]. Additionally, when the original therapeutic target was systemic, examination of blood-brain barrier (BBB) permeability may not have been essential during initial drug development for the primary indication. Given that most AD treatments necessitate BBB penetration, Phase I investigations might be required to determine cerebral accessibility of the potential therapeutic agent [5]. Beyond intellectual property concerns, researchers have identified additional complications associated with developing repurposed pharmaceuticals for novel therapeutic applications, including limited availability of historical trial data and insufficient transparency regarding clinical study outcomes for the original indication. International pharmaceutical databases documenting drug properties and therapeutic effects have been proposed as a potential solution to address data accessibility limitations [5,11,24].

FUTURE PERSPECTIVES OR DIRECTIONS

Given that etiological and clinical diversity represents a characteristic feature of AD, no single therapeutic agent is suitable for all individuals with AD. Characterizing AD across network, cellular, genetic, and molecular dimensions will enable more personalized treatment approaches [40]. Traditionally, AD research and development has concentrated on neurodegeneration; however, with growing recognition of AD as a condition with diverse variants where causative genes, susceptibility genes, mutation sites, and disease modifiers exhibit substantial variation, establishing a research environment and funding framework that supports pharmaceutical development targeting multiple mechanisms of action becomes essential [41].

Further advancements in this field should prioritize the continued convergence of computational approaches with experimental verification. This encompasses

enhancing mathematical frameworks to achieve superior alignment with empirical observations, leveraging multi-modal datasets for comprehensive disease characterization, and exploring artificial intelligence capabilities for early identification and personalized therapeutic approaches [19]. The results underscore the significance of computational models in replicating complex biological mechanisms, forecasting treatment effectiveness, and elucidating pharmacodynamic relationships among disease-related proteins. Computational drug repositioning methodologies possess the capacity to accelerate pharmaceutical development while substantially reducing temporal and financial investments required for neurodegenerative disease therapeutics.

CONCLUSION:

AD represents a neurodegenerative condition marked by the gradual deterioration of cognitive functions stemming from multiple pathological factors. Given that etiological and clinical diversity constitutes a fundamental characteristic of AD, no singular therapeutic agent proves suitable for the entire AD patient population. Consequently, pharmaceutical repurposing for AD has been pursued through diverse approaches, encompassing target-oriented medications, network-based methodologies, transcriptomics-driven strategies, molecular docking techniques, and computational repurposing methods. DR approaches incorporate anti-diabetic agents such as insulin, metformin, liraglutide, and dapagliflozin, anti-hypertensive medications including losartan, telmisartan, candesartan, amlodipine, and prazosin, along with antidepressants comprising SSRI'S, tricyclic antidepressants, and certain antimicrobial agents that participate in pathophysiological mechanisms involving extracellular amyloid- β 42 (A β 42) plaque accumulation and Tau hyperphosphorylation, which generates intracellular neurofibrillary tangles (NFTs) resulting in oxidative stress, mitochondrial impairment, neuroinflammation, excitotoxicity, and insulin signaling disruption, ultimately causing neuronal apoptosis and cellular death. Additionally, pharmaceutical repurposing for AD encompasses machine learning and AI technologies, which assume a crucial function in developing innovative therapeutic approaches.

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All are contributed equally.

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