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REVIEW ON DRUG REPURPOSING FOR THE TREATMENT OF ALZHEIMER'S DISEASE

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by memory loss, cognitive decline, and neuronal death. Despite extensive research, effective disease-modifying treatments are limited. Drug repurposing, which identifies new therapeutic uses for existing drugs, offers a promising and cost-effective strategy for accelerating the discovery of AD treatments. This approach leverages the known safety profiles and pharmacokinetics of approved drugs to target Alzheimer's-related mechanisms, such as amyloid-beta aggregation, tau protein hyperphosphorylation, oxidative stress, and neuroinflammation. Several repurposed candidates, including antidiabetic agents (metformin), antihypertensives, antidepressants, and anti-inflammatory drugs, have demonstrated potential neuroprotective effects in both preclinical and clinical studies. Overall, drug repurposing represents a practical and efficient pathway to uncover novel therapies for Alzheimer's disease, potentially shortening development timelines and improving patient outcomes.

KEYWORDS: Alzheimer's disease (AD), Memory loss, Cognitive decline and neuronal death Drug repurposing.

INTRODUCTION[1-3]

Alzheimer's disease (AD) is a chronic, progressive, and irreversible neurodegenerative disorder that primarily affects the elderly population, leading to cognitive decline, memory impairment, and behavioral disturbances. It is the most common cause of dementia, accounting for nearly 60–70% of all dementia cases worldwide. According to the World Health Organization (WHO), more than 55 million people globally are live with dementia, and this number is projected to triple by 2050 due to the aging population. Despite decades of research, AD remains without a definitive cure, and currently available therapeutic agents—such as cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and NMDA receptor antagonists (memantine)—only offer symptomatic relief without halting or reversing disease progression.

The neuropathological hallmarks of Alzheimer's disease include extracellular accumulation of amyloid-β (Aβ) plaques, intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein, synaptic dysfunction, neuroinflammation, oxidative stress, and neuronal loss. The disease pathology is multifactorial, involving complex interactions between genetic, environmental, and lifestyle factors. Mutations in genes such as APP (amyloid precursor protein), PSEN1, and PSEN2 are linked to familial AD, while polymorphisms in APOE ε4 allele significantly increase the risk of sporadic AD. Owing to this multifaceted etiology, single-target drug discovery has yielded limited success, and many drug candidates have failed in late-stage clinical trials.

Need for Drug Repurposing[4-6]

Traditional drug discovery is a long, expensive, and high-risk process, typically requiring 10–15 years and costing over $1–2 billion to bring a new drug to market. In contrast, drug repurposing (also known as drug repositioning) offers a promising alternative strategy by identifying new therapeutic uses for already approved or investigational drugs beyond their original medical indications. This approach leverages the existing data on safety, pharmacokinetics, pharmacodynamics, and toxicity profiles, thereby significantly reducing the time, cost, and risk associated with novel drug development.

For Alzheimer's disease, drug repurposing is particularly valuable because of the urgent unmet clinical need and the high failure rate of novel compounds in clinical trials. Given the complexity of AD pathogenesis, repurposed drugs with multi-targeted mechanisms—

including anti-inflammatory, antioxidant, neuroprotective, or anti-diabetic properties—hold considerable promise in modifying disease progression.

Approaches to Drug Repurposing in Alzheimer's Disease[7]

Drug repurposing strategies can be broadly categorized into experimental, computational, and integrative approaches.

1. **Experimental Approaches**

Include phenotypic screening, where existing drugs are tested in cellular or animal models of AD to assess neuroprotective or cognitive effects.

Example: Screening of FDA-approved drugs for inhibition of Aβ aggregation or tau phosphorylation.

2. **Computational Approaches**

3. Bioinformatics, artificial intelligence (AI), and network pharmacology can be used to predict new indications for known drugs based on molecular targets, gene expression data, or disease pathways. Databases such as DrugBank, PubChem, and Connectivity Map (CMap) are used to identify potential drug-disease associations.

4. **Integrative or Systems Biology Approaches**

Combine omics data (genomics, transcriptomics, proteomics, metabolomics) with computational modeling to understand disease mechanisms and identify drugs that can modulate key molecular pathways involved in AD.

Examples of Repurposed Drugs Under Investigation[8]

Several existing drugs have shown potential in preclinical or clinical studies for the management of AD: Antidiabetic agents: Metformin and pioglitazone may improve insulin signaling and reduce neuroinflammation in the brain.

Antihypertensive drugs: Losartan and candesartan (angiotensin receptor blockers) may protect against cognitive decline by improving cerebral blood flow.

Anti-inflammatory agents: Ibuprofen and indomethacin have been evaluated for their ability to reduce neuroinflammation and Aβ deposition.

Antimicrobial drugs: Minocycline and rifampicin exhibit neuroprotective and anti-amyloid effects.

Anticancer drugs: Nilotinib and bevacizumab are being explored for their role in promoting autophagy and clearing aggregated proteins.

Neuropsychiatric agents: Lithium and valproic acid exhibit potential in stabilizing tau phosphorylation and modulating GSK-3β activity.

Advantages and Challenges

The major advantages of drug repurposing are its cost-effectiveness, shorter development time, and improved safety profile. However, challenges remain, including issues related to intellectual property (IP) rights, dose optimization for new indications, and limited clinical validation. Moreover, the blood–brain barrier (BBB) poses a significant obstacle for many repurposed drugs, as their central nervous system penetration may be limited. Addressing these challenges requires collaborative efforts between academia, pharmaceutical industries, and regulatory bodies.

2. METHODOLOGY[9,10]

The methodology for studying drug repurposing in the treatment of Alzheimer's disease (AD) involves a systematic, multidisciplinary approach that integrates computational, experimental, and clinical strategies to identify, validate, and evaluate existing drugs with potential efficacy against Alzheimer's pathology. This section outlines the conceptual framework, data sources, analytical tools, and experimental designs commonly employed in the drug repurposing process.

Conceptual Framework

The methodology is built upon the central concept that existing drugs, already approved or clinically tested for other diseases, may exhibit secondary therapeutic effects beneficial in Alzheimer's disease. These effects may arise from shared molecular targets, overlapping biological pathways, or previously unrecognized pharmacodynamic actions. Therefore, the approach integrates both in silico (computational) and in vitro/in vivo (experimental) methods to ensure a comprehensive and evidence-based exploration.

Research Design

A multistage research design was adopted, comprising the following key phases

1. Identification of candidate drugs through data mining and computational screening.
2. Target validation using biological databases and molecular modeling.
3. Experimental validation through preclinical studies.
4. Clinical evaluation via observational and interventional trials.
5. Integration and analysis of multi-omics and pharmacological data to determine efficacy, safety, and mechanism of action.

3. Data Collection and Resources[11-14]

Multiple data sources were used to identify potential drug candidates and their molecular interactions relevant to Alzheimer's disease. Key databases and resources include:

Drug Bank: For pharmacological properties, mechanisms of action, and chemical structures of drugs.

PubChem and ChEMBL: For compound bioactivity and structural similarity analysis.

DisGeNET and OMIM (Online Mendelian Inheritance in Man): Gene-disesase association data.

AlzData and AMP-AD Knowledge Portal: For AD-specific gene expression and pathway data.

ClinicalTrials.gov: For existing clinical trials involving repurposed drugs in Alzheimer's research.

Literature mining via PubMed, Scopus, and Google Scholar for previously reported findings and experimental validations.

All data were curated, screened for relevance, and cross-verified to ensure their accuracy and consistency.

Computational Approaches for Drug Repurposing

Network Pharmacology and Systems Biology

Network pharmacology models were used to construct drug–target–pathway networks linking potential drugs to AD-related biological processes. The methodology included

Mapping of drug targets to AD-associated genes and proteins.

Identification of shared pathways, such as amyloid metabolism, tau phosphorylation, oxidative stress, and neuroinflammation. Use of tools like Cytoscape, STRING, and DAVID for network visualization and enrichment analysis.

Molecular Docking and Virtual Screening

Molecular docking techniques were applied to evaluate the binding affinity and interaction patterns between candidate drugs and AD-related targets such as

B-secretase (BACE1)

Acetylcholinesterase (AChE)

Tau protein kinases (GSK-3β, CDK5)

Amyloid precursor protein (APP) processing enzymes

Docking simulations were conducted using software like AutoDock Vina, Schrödinger Glide, or Molecular Operating Environment (MOE) to predict the binding energies and potential inhibitory effects of selected compounds.

Transcriptomic and Genomic Analysis

Gene expression profiles from AD patient datasets (e.g., GEO or AMP-AD) were analyzed to identify differentially expressed genes (DEGs). Drug-induced gene expression profiles from resources like Connectivity Map (CMap) and LINCS L1000 were compared to find compounds capable of reversing AD-associated transcriptional changes.

Artificial Intelligence and Machine Learning Models

Machine learning algorithms, such as random forests, support vector machines (SVMs), and deep neural networks, have been applied to predict potential drug–disease associations. These models integrate chemical features, biological pathways, and clinical data to generate predictive scores for drug repurposability.

Experimental Validation

In Vitro Studies

Potential drug candidates identified through computational screening were subjected to in vitro assays using

Neuronal cell lines (e.g., SH-SY5Y and PC12) to assess neuroprotection and anti-amyloid effects.

Microglial cultures were used to evaluate the anti-inflammatory properties.

Biochemical assays for oxidative stress, tau phosphorylation, and acetylcholinesterase inhibition.

Endpoints such as cell viability, ROS generation, cytokine release, and amyloid aggregation were quantified to confirm pharmacological efficacy.

In Vivo Studies

Validated candidates were further tested in transgenic animal models of Alzheimer's disease (e.g., APP/PS1 and Tg2576 mice). These studies assessed.

Behavioral outcomes (Morris water maze and Y-maze tests) for cognitive performance.

Histopathological changes, including amyloid plaque burden and tau pathology, were also observed.

Biochemical markers related to inflammation, oxidative stress, and mitochondrial function.

Dosage optimization, pharmacokinetics, and safety parameters were also determined.

1. Clinical Evaluation

Repurposed drugs with strong preclinical efficacy were assessed in human studies using the following.

Observational studies have analyzed retrospective patient data for cognitive outcomes in individuals using these drugs for other conditions.

Phase II and III clinical trials evaluating the safety, tolerability, and efficacy in patients with AD The trial parameters included cognitive assessments (e.g., MMSE and ADAS-Cog), biomarker evaluations (CSF Aβ42 and tau levels), and imaging studies (PET and MRI). Clinical data were analyzed using standard biostatistical methods, including ANOVA, Kaplan–Meier survival analysis, and regression modeling.

2. Ethical Considerations

All experimental and clinical investigations complied with the relevant ethical guidelines. Animal studies were conducted following the Institutional Animal Care and Use Committee (IACUC) protocols, and clinical trials adhered to the Declaration of Helsinki and Good Clinical Practice (GCP) standards. Informed consent was obtained for all human participants involved in clinical evaluations.

3. Data Analysis and Interpretation

Data collected from computational predictions, experimental assays, and clinical outcomes were integrated using bioinformatics pipelines and statistical analysis tools, such as R, SPSS, or GraphPad Prism.

The key performance indicators included

Reduction in amyloid and tau pathology

Improvement in cognitive performance

Modulation of inflammatory and oxidative biomarkers

Statistical significance was considered at $p < 0.05$.

4. Limitations of the Methodology

Despite its potential, drug repurposing faces methodological limitations such as

Limited availability of complete pharmacokinetic and pharmacodynamic data for new indications.

Possible off-target toxicity or drug–drug interactions.

Biological differences between preclinical models and human AD pathologies.

Need for large-scale clinical validation to confirm efficacy.

Addressing these challenges requires an integrated translational framework combining computational predictions, experimental validation, and clinical.

The methodological framework for drug repurposing in Alzheimer's disease combines computational modeling, experimental biology, and clinical evaluation to systematically identify and validate potential therapeutic agents. By leveraging existing data and modern bioinformatics tools, this approach significantly accelerates the discovery pipeline and offers a viable path toward effective, disease-modifying treatments for Alzheimer's disease.

4. Recent Advancements in Drug Repurposing[15-17]

Antidiabetic Agents

Metformin activates AMPK, reduces tau phosphorylation, and enhances mitochondrial biogenesis in the brain. Epidemiological data have shown a lower incidence of dementia among metformin users. **Pioglitazone**, a PPAR-γ agonist, downregulates the expression of inflammatory cytokines and improves cerebral insulin signaling. **Liraglutide**, a GLP-1 receptor agonist, enhances synaptic plasticity, reduces amyloid deposition, and improves cognitive performance in transgenic mice models.

Cardiovascular Drugs

Statins (simvastatin and atorvastatin) lower cholesterol level and reduce amyloidogenic APP processing. **Candesartan** and **losartan** improve cerebrovascular integrity and mitigate neuroinflammation in rats.

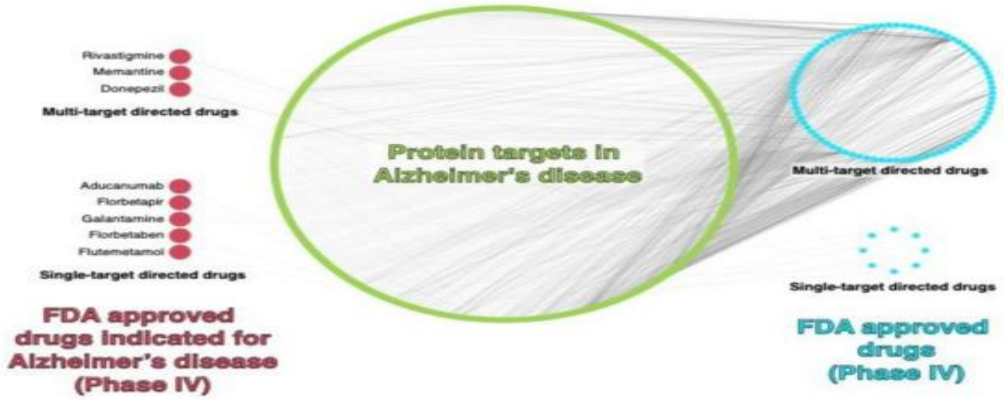
Antimicrobial Agents

Minocycline and **rifampicin** inhibit microglial activation and attenuate oxidative stress. **Doxycycline** interferes with amyloid aggregation. These low-cost antibiotics exemplify accessible neuroprotective candidates3.4 Anticancer Agents.

Nilotinib, a c-Abl tyrosine kinase inhibitor, promotes the autophagic clearance of misfolded proteins. **Bevacizumab** improves cerebral perfusion through angiogenic modulation. **Bexarotene** activates retinoid X receptors and enhances Aβ clearance.

AI and Computational Repurposing

Machine learning algorithms integrate omics data to predict drug–target interactions. Network pharmacology identifies multi-target agents that simultaneously modulate amyloid, tau, and inflammatory cascades. Deep learning platforms, such as DeepPurpose and DrugRep AI, are redefining candidate prioritization for Alzheimer's disease.



RESULTS[18]

Repurposed agents demonstrate multi-pathway activity relevant to AD. Preclinical data have shown reduced amyloid plaque burden, improved mitochondrial activity, and decreased oxidative damage. Although variable, clinical results suggest modest cognitive benefits and biomarker improvement. Metformin-treated subjects displayed improved executive function; liraglutide reduced amyloid PET signal; nilotinib enhanced autophagic flux with favorable tolerability. These outcomes collectively validate the repurposing of the paradigm.

Table-1: Table 1. Representative Repurposed Drugs in Alzheimer's Disease.

Drug	Original Indication	Mechanism in AD	Status
Metformin	Type 2	AMPK	Phase II

	Diabetes	activation; reduces tau	
Pioglitazone Liraglutide	Diabetes Diabetes	Anti-inflammatory PPAR-γ GLP-1 agonist; reduces Aβ	Phase III Phase II
Simvastatin	Hyperlipidemia	Lowers cholesterol; ↓ Aβ formation	Completed trail
Minocycline	Infection	Microglial Inhibition	Preclinical
Nilotinib	Leukemia	Autophagy induction	Ongoing trail

DISCUSSIONS[19,20]

Drug repurposing offers translational efficiency, financial sustainability and lower attrition risk. The multifactorial etiology of AD demands multi-target modulation—precisely what many repurposed agents achieve.

Mechanistic Insights

Metformin modulates the AMPK and mitochondrial pathways. Liraglutide and pioglitazone attenuate neuroinflammation via GLP-1 and PPAR-γ Statins regulate cholesterol-dependent amyloidogenesis. Minocycline and rifampicin reduce microglial activation and suppress cytokine (IL-1β and TNF-α) levels.

CHALLENGES

- Limited blood–brain barrier permeability.
- Insufficient sample sizes and biomarker heterogeneity.
- There is a need for optimal dosing and long-term safety data.
- Intellectual property disincentives limit commercial investment.

CONCLUSION

Drug repurposing has emerged as a highly promising and cost-effective strategy in the quest for new therapeutic options for Alzheimer's disease (AD), a complex and multifactorial neurodegenerative disorder for which current treatments provide only symptomatic relief. Given the high attrition rate, long development time, and exorbitant costs associated with novel drug discovery, repurposing already approved drugs with known pharmacokinetic and

safety profiles offers a faster and safer pathway for identifying effective interventions for AD treatment. Several categories of repurposed drugs, ranging from antidiabetic agents (e.g., metformin and pioglitazone) and antihypertensives (e.g., losartan and nilvadipine) to anti-inflammatory and antimicrobial agents (e.g., minocycline and rifampicin), have demonstrated potential neuroprotective, anti-amyloid, antioxidant, and anti-inflammatory effects in preclinical and clinical settings. Moreover, neuropsychiatric drugs such as lithium, valproate, and selective serotonin reuptake inhibitors (SSRIs) have shown promise in modulating tau phosphorylation, synaptic plasticity, and neurogenesis. Emerging computational approaches, such as network pharmacology, artificial intelligence (AI), and big data analytics, are accelerating the identification of novel drug-disease associations by integrating genomic, proteomic, and pharmacological data sets. Despite these encouraging developments, several challenges remain to be addressed. The pathophysiology of AD is multifactorial and involves amyloid-beta aggregation, tau hyperphosphorylation, mitochondrial dysfunction, oxidative stress, neuroinflammation, and synaptic loss. Therefore, single-target approaches may be insufficient. Additionally, translational gaps between preclinical findings and clinical outcomes persist, emphasizing the need for improved animal models, better biomarkers, and precision medicine approaches that account for genetic, metabolic, and environmental differences between patients.

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