Advancing Alzheimer's disease research and drug discovery through the use of artificial intelligence

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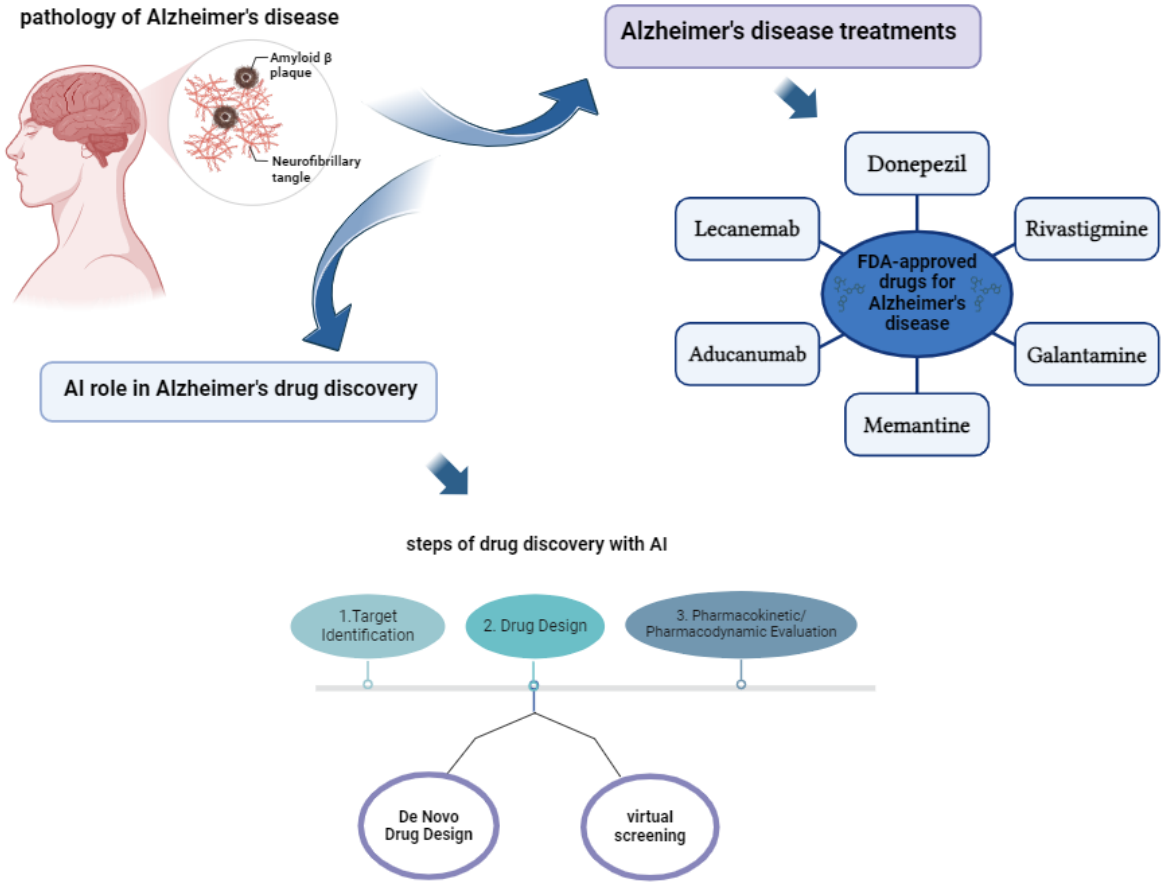
Abstract

Artificial intelligence (AI) and machine learning (ML) have revolutionized Alzheimer's disease (AD) research, driving advancements in both diagnosis and drug discovery. AI-based models, such as convolutional neural networks (CNNs) and support vector regression (SVR), have demonstrated high precision in differentiating between AD, mild cognitive impairment (MCI), and healthy individuals through neuroimaging techniques like MRI and PET. These technologies have enhanced the detection of early AD biomarkers, aiding in more accurate diagnosis. In drug discovery, AI-driven methods like machine learning and deep learning are transforming key processes such as virtual screening, de novo drug design, and pharmacokinetic/pharmacodynamic (PK/PD) modeling. AI plays a crucial role in predicting drug properties related to absorption, distribution, metabolism, excretion, and toxicity (ADMET), particularly in evaluating blood-brain barrier (BBB) penetration. Models like support vector machines (SVM) and light gradient boosting machine (LightGBM) have achieved high accuracy in predicting BBB permeability, accelerating the development of therapeutic candidates. Furthermore, AI integration in multiomic data analysis, utilizing public datasets like ADNI and NIAGADS, has enabled the identification of key genes and pathways involved in AD, which serve as potential drug targets. Advanced machine learning techniques, including logistic ridge regression, random forest, and support vector machines, have identified critical pathways like mitochondrial dysfunction and NF-kappa B signaling in AD pathogenesis. Overall, AI has been pivotal in AD research, improving early diagnosis and expediting drug discovery, offering promising avenues for future treatments and precision medicine.

Keywords: artificial intelligence, Alzheimer's disease, drug discovery, multi-omics analyses, machine learning



Graphic Abstract of the Review on AI roles in Alzheimer's Disease Treatments

1. Introduction

Dementia is a severe decline in cognitive abilities that significantly affects a person's daily activities. Alzheimer's disease (AD) is the leading cause of the aging-related cognition decline, accounting for 60-80% of all the dementia. AD typically occurs after the age of 65, at which point it is known as late-onset AD (LOAD). In contrast, early-onset AD (EOAD), which occurs before the age of 65, is a rare AD form affecting about 5% of the AD patients. EOAD often presents with atypical symptoms, leading to delayed diagnosis and more aggressive disease progression. AD is a neurodegenerative disorder characterized by a gradual onset and progressive decline in behavioral and cognitive functions, including memory, comprehension, language, attention, reasoning, and judgment. Although AD itself is not a direct cause of death, it significantly increases susceptibility to other fatal complications. Currently, nearly 44 million people worldwide suffer from AD, and there is no cure and limited treatment available. Existing

drugs can only slow the progression of memory and cognitive decline, highlighting the urgent need for new therapies to reverse cognitive impairment.[1], [2], [3]

2. Pathology of AD

AD is known for the harmful build-up of amyloid plaques outside brain cells and tangled tau proteins inside them. These abnormalities are key to understanding the disease and are a major focus of research. In 1984, George G. Glenner and Caine W. Wong discovered that the main substance in these plaques is amyloid β protein (Aβ)[4], [5], [6]. Aβ is formed when a larger protein called amyloid precursor protein (APP) is cut into smaller pieces by two enzymes, β-secretase (BACE1) and γ-secretase. This process is a part of what is known as the amyloidogenic pathway, which leads to the production of Aβ peptides, particularly $A\beta_{38}$, $A\beta_{40}$, and $A\beta_{42}$. However, when APP is first cleaved by another enzyme, α-secretase, Aβ does not form, which is a part of the non-amyloidogenic pathway. In this pathway, APP is cleaved at a specific site, producing a fragment incompatible with the Aβ production.[7] [8], [9], [10]

Maintaining a balance between Aβ production and clearance is critical to prevent toxic accumulation of aggregated Aβ species. Aβ is cleared from the brain by several methods, including degradation by enzymes, crossing the blood-brain barrier (BBB), movement through the interstitial fluid (ISF), and absorption into the cerebrospinal fluid (CSF)[11]. The BBB, made up of tightly packed endothelial cells, controls what enters and leaves the brain. Aβ moves from the brain into the blood via specific transporters, such as low-density lipoprotein receptor-related protein 1 (LRP-1) and ABC transporters (ABCA1 and ABCB1). Conversely, receptors for advanced glycosylation end products (RAGE) help Aβ get into the brain. In AD, the transporters that remove Aβ from the brain are less active, while those that bring Aβ into the brain are more active, upsetting the balance[10], [11], [12]. Clearance of Aβ by the perivascular drainage system is critical. Failure of this system can lead to problems with synaptic function and cognitive ability, contributing to AD. The clearance of Aβ via CSF depends on the production of CSF, the integrity of the blood-CSF barrier, relevant transporters, and lymphatic absorption. In AD, the blood-CSF barrier is damaged, impairing Aβ clearance[10], [13], [14], [15] (**Supplementary Figure 1**).

Several enzymes are involved in the degradation of Aβ, including zinc metalloendopeptidases, insulin-degrading enzyme (IDE), matrix metalloproteinases (MMPs), angiotensin-converting enzyme (ACE), endothelin-converting enzyme (ECE), serine proteases, cysteine proteases, and

kallikrein-related peptidase 7. In patients with AD, the activity of some of these enzymes, such as IDE, ACE, and neprilysin (NEP), is reduced in the hippocampus. Animal models also show impaired Aβ degradation. GWAS studies have identified risk factors for AD, such as RIN3, CLU, and PTK2B, that are associated with these degradation pathways[10], [12], [16].

The "amyloid hypothesis" proposes that Aβ production triggers a series of harmful events leading to AD. This includes inflammation, oxidation, excessive glutamate activity (excitotoxicity), and tau protein hyperphosphorylation. Normally, tau protein helps stabilizing the neuron structure, but when it becomes hyperphosphorylated, it forms insoluble tangles, disrupting neuron function and transport. This contributes to neurodegeneration. Initially, tau hyperphosphorylation was thought to be a consequence of Aβ deposition, but now it is believed that Aβ and tau may act independently yet synergistically, each worsening the other's toxic effects. As AD progresses, it destroys neurons, leading to imbalances in neurotransmitters like acetylcholine, dopamine, and serotonin, which results in the cognitive deficits typical of the disease.[10], [11], [12], [17]

Understanding AD involves exploring various theories, one of which is the mitochondrial dysfunction hypothesis. This theory suggests that mitochondrial dysfunction in an AD brain leads to amyloidosis, cell cycle reentry, and tau phosphorylation. In addition, there is strong evidence that both the cholinergic and glutamatergic neurochemical systems play a significant role in AD. The cholinergic system, essential for memory and learning, is compromised early in AD due to the loss of neurons or their ability to produce acetylcholine (ACh). This leads to a decrease in ACh levels and function, which are critical for cognitive processes. Alongside this cholinergic deficit, there are other presynaptic issues, such as the loss of cholinergic neural networks and reduced acetylcholinesterase activity. The cholinergic theory of AD emphasizes that these impairments are major contributors to the cognitive decline observed in patients. The glutamatergic system, primarily involving N-methyl-d-aspartate (NMDA) receptors, also plays a critical role in memory and learning. Glutamate, an excitatory neurotransmitter, interacts with NMDA receptors to support these cognitive functions. However, excessive activation of NMDA receptors by glutamate can cause excitotoxicity, leading to neuronal damage and contributing to the neurodegenerative processes seen in AD. Glutamatergic neurons are the most numerous in the central nervous system (CNS), and their loss contributes significantly to the brain shrinkage characteristic of AD.[12], [18], [19], [20], [21]

3. Comorbidities of AD

AD is closely associated with various cardiovascular risk factors. Midlife hypertension has been found to significantly increase the risk of late-life dementia, including AD, as shown in the cohort study. This relationship is potentially due to long-standing hypertension leading to endothelial dysfunction, arterial stiffness, and atherosclerosis, which collectively contribute to cerebral hypoperfusion. Additionally, hyperlipidemia has been strongly linked to AD, with studies indicating that high midlife cholesterol levels and imbalances in HDL and LDL levels exacerbate the risk. The APOE4 allele, which is linked to AD susceptibility, often corresponds with elevated cholesterol levels, influencing the activity of brain secretase enzymes and increasing Aβ production. The use of statins has been observed to reduce AD occurrence, although the exact mechanisms remain unclear[22], [23].

Type 2 diabetes mellitus (DM2) and prediabetic conditions also elevate the risk for dementia, including vascular dementia and AD. DM2 is known to cause cerebral microvascular damage and contribute to endothelial dysfunction and atherosclerosis. Hyperinsulinemia, typical in DM2, may interfere with the insulin-degrading enzyme (IDE), which is responsible for degrading both insulin and Aβ. Consequently, higher insulin levels can lead to increased Aβ accumulation. Other lifestyle-related risk factors such as smoking, obesity, and sedentary behavior are similarly associated with the development of both cardiovascular disease (CVD) and AD. Gender differences also play a role, with women showing a higher susceptibility to AD when they have cardiovascular risk factors compared to men[23], [24], [25].

In addition to cardiovascular and metabolic disorders, other health conditions have been implicated in increasing AD risk. Depression and anxiety, while risk factors for dementia, might also be early symptoms of the disease. Hearing loss has been identified as a potential risk factor, though a direct causal link remains to be confirmed. Emerging research has also highlighted the significance of conditions like constipation, spondylosis, and abnormal weight loss as potential predictors of AD. Specifically, cervical spondylosis might affect blood flow or cerebrospinal fluid dynamics, accelerating neurodegeneration. Furthermore, sleep disorders, hypothyroidism, and certain cancers have shown associations with AD, suggesting a complex interplay of genetic and environmental factors in the disease's progression[23]

Moreover, recent studies have explored the connection between COVID-19 and AD, revealing significant neurological implications. Although SARS-CoV-2 primarily affects the respiratory system, over 30% of hospitalized COVID-19 patients exhibit neurological symptoms. Severe

COVID-19 cases in elderly individuals often involve a cytokine storm, leading to excessive inflammation and immune responses that may accelerate brain inflammatory neurodegeneration. Both AD and COVID-19 share common risk factors and pathogenetic mechanisms, potentially explaining the higher incidence and mortality rates among AD patients infected with COVID-19. Additionally, the isolation and quarantine measures to prevent COVID-19 spread can negatively impact AD patients, increasing cognitive decline due to reduced social interaction.[26], [27], [28], [29]

4. Pharmacotherapeutic approaches in AD

While AD remains incurable, certain treatments can help slow the progression of clinical decline and improve cognitive function and daily living skills. In addition, other treatments may provide temporary relief from symptoms such as memory loss and confusion. Over the past few decades, significant efforts have been made to develop disease-modifying treatments (DMTs) for AD, focusing on the underlying mechanisms that cause neuronal damage and progressive dementia. The U.S. Food and Drug Administration (FDA) has approved medications in two main categories: those that may slow the clinical worsening of AD and those that provide short-term symptom relief[13], [30].[31]

4.1. Anti-Aβ drugs

A prominent target for these treatments is the aggregation of beta-amyloid (Aβ) peptides in the brain. However, few anti-Aβ drugs have demonstrated significant cognitive benefits in clinical trials. Currently, several anti-Aβ agents, including aducanumab, lecanemab, gantenerumab, donanemab, and BACE inhibitors, are under investigation. The FDA has approved two anti-Aβ mAbs, aducanumab and lecanemab, representing a significant step forward[32], [33], [34], [35], [36].

In 2021, the FDA granted conditional accelerated approval to Biogen's aducanumab, an antibody designed to reduce amyloid burden. However, phase 3 trials yielded inconsistent results, and the drug was criticized for its high cost and potentially serious side effects, leading to limited use in the U.S. In addition, the European Medicines Agency (EMA) did not approve aducanumab due to inconsistent efficacy and safety concerns[32], [34], [35].

Another amyloid-targeting antibody, lecanemab, is designed to reduce brain amyloid burden by targeting protofibrils, an intermediate step in amyloid plaque formation. Lecanemab received accelerated approval from the FDA in January 2023 after promising results in Phase 2 trials. Recent Phase 3 studies showed significant effects on clinical outcomes, including a 27% reduction in progression on the Clinical Dementia Rating-Sum of Boxes (CDR-SB). Despite these positive results, lecanemab also showed some side effects, such as infusion-related reactions and amyloid-related imaging abnormalities with edema or effusion (ARIA-E). A supplemental Biologics License Application for traditional approval has been submitted to the FDA and approval by the EMA is expected based on the results of the Phase 3 trial[32], [37], [38], [39].

4.2. Acetylcholinesterase Inhibitors

Acetylcholinesterase, commonly known as AChE, is a key enzyme in the body's cholinergic nervous system, which includes both the peripheral and central nervous systems. AChE breaks down acetylcholine (ACh) into choline and acetate ions through a process called hydrolysis. The active site of AChE is a large, hydrophobic cavity divided into two parts: the esteratic subsite (ES) and the anionic substrate binding site (AS). In the central nervous system, acetylcholine is an important neurotransmitter. It binds to the AS with its positively charged quaternary amine, allowing this site to interact with other similar substrates and inhibitors. The FDA has approved four acetylcholinesterase inhibitors (AChEIs) for the treatment of AD: donepezil and rivastigmine for mild to severe AD, galantamine for mild to moderate AD, and tacrine for mild to moderate AD (Figure 1). In people with AD, the enzyme acetylcholinesterase becomes more active, breaking down acetylcholine—a key neurotransmitter for memory and learning—faster than usual, leading to lower levels in the brain. This enzyme also plays a role in the formation of the amyloid plaques and neurofibrillary tangles that are hallmarks of AD. By inhibiting acetylcholinesterase, these drugs increase acetylcholine levels in the brain, helping to alleviate symptoms in those with mild to moderate AD. Most patients tolerate these drugs well[12], [19], [40], [41].

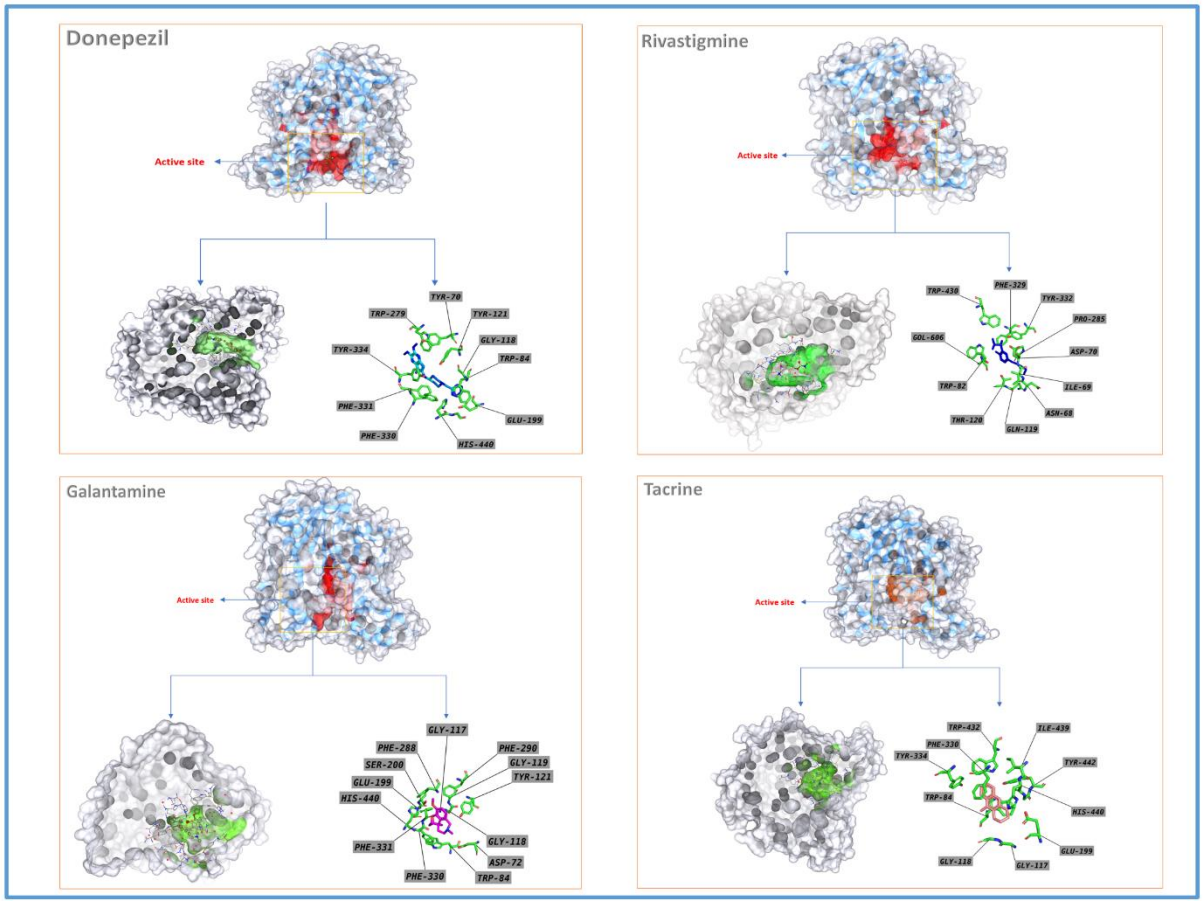


Figure 1. Structural representations of donepezil, galantamine, rivastigmine, and tacrine with acetylcholinesterase. The key amino acid residues involved in binding for each inhibitor include: **Donepezil:** Interacts with residues TYR-70, TRP-279, GLY-118, PHE-330, PHE-331, and HIS-440, contributing to its inhibitory effect. **Rivastigmine:** Forms key interactions with ASP-70, GLN-119, TRP-82, TYR-332, ASN-68, and THR-120. **Galantamine:** Engages with GLY-117, GLY-118, GLU-199, ASP-72, PHE-288, PHE-300, PHE-331, HIS-440, TRP-84, and TYR-121. **Tacrine:** Binds to residues GLY-117, GLY-118, GLU-199, ASP-72, PHE-330, HIS-440, TRP-84, TRP-432, TYR-442, and TYR-432.

Common side effects of these drugs are gastrointestinal issues, such as diarrhea, nausea, and vomiting. Donepezil and galantamine are mainly processed by the liver, while rivastigmine is metabolized by both the liver and intestines. Donepezil and galantamine specifically and reversibly inhibit acetylcholinesterase, whereas rivastigmine acts as a "pseudo-irreversible" inhibitor of both acetylcholinesterase and butyrylcholinesterase. This means rivastigmine forms a stable complex with the enzyme, preventing it from breaking down acetylcholine. Tacrine is quite effective at inhibiting both AChE and butyrylcholinesterase (BChE) enzymes. However, its use is restricted because of numerous side effects such as nausea, vomiting, loss of appetite, diarrhea, and clumsiness. Moreover, patients on tacrine need regular blood tests because it can cause liver damage. To maintain its therapeutic effects, multiple doses are necessary due to tacrine's short half-life and the risk of severe side effects at higher doses. Because of these issues, particularly its liver toxicity, tacrine was eventually discontinued. Galantamine has a half-life of 6 to 8 hours, while donepezil's half-life is much longer at 70 hours. Rivastigmine, despite its shorter half-life, has prolonged effects[12], [18], [40].

4.3. Glutamate Inhibitor

Excitotoxicity is a condition where excessive glutamate activity causes neuronal damage by increasing calcium levels in neurons. Memantine, a non-competitive NMDA receptor antagonist (Figure 2), helps to counteract the harmful effects of high glutamate levels in the brain. This characteristic has made memantine an effective treatment for individuals with AD. Approved for moderate to severe AD, memantine has been shown to improve cognitive function and outcomes in patients. Generally, patients tolerate memantine well, though it can cause minor and temporary side effects and may interact with other medications. Memantine can be used in combination with AChEIs because their mechanisms are complementary. This combination therapy often benefits patients by producing better results without increasing side effects. For people with moderate to severe dementia, using memantine alone or in combination with AChEIs at higher doses may lead to better overall functioning and therapeutic outcomes. However, combining memantine with other NMDA receptor antagonists, such as amantadine, budipine, ketamine, and dextromethorphan, may result in pharmacotoxic psychosis. Common side effects seen in clinical trials include dizziness, agitation, hallucinations, headache, and fatigue, while less common symptoms include anxiety, vomiting, urinary tract infection, and increased sweating[18], [42], [43], [44], [45].

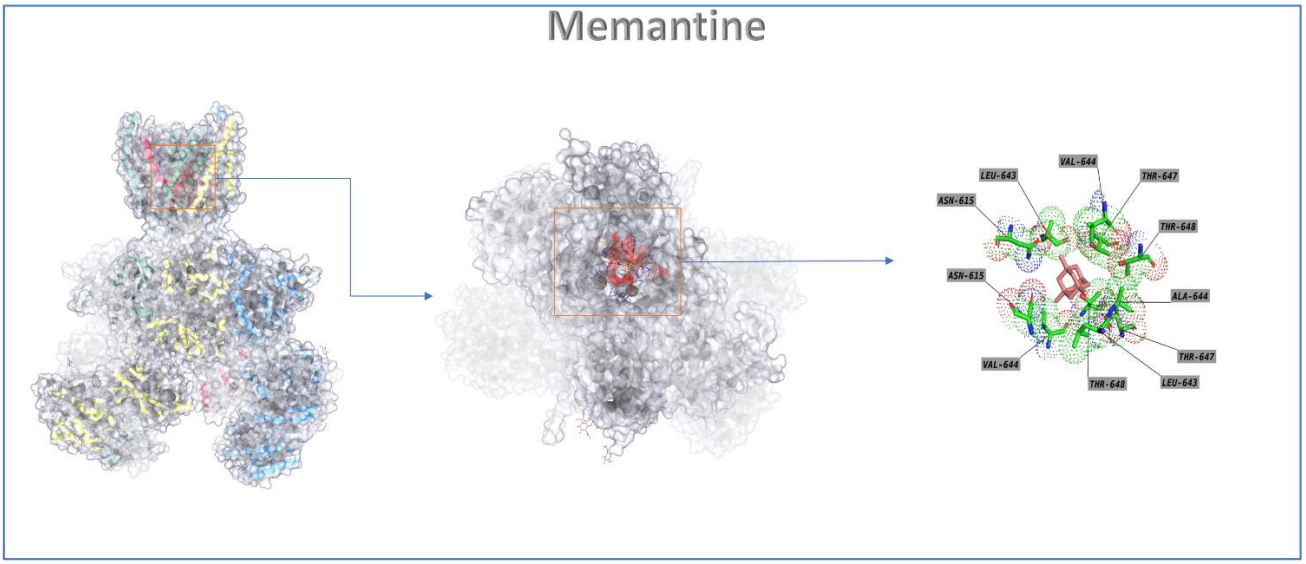


Figure 2. Structural representations of Memantine bound to the NMDA receptor. The key amino acid residues involved in binding for each inhibitor include: VAL-644, ALA-644, THR-647, THR-648, LEU-643 and ASN-615.

Table 1. Overview of patient demographics, dosing, and treatment duration in FDA-approved AD drug trials

Medicine name	Patients Group		Placebo Group		Age		Dose		Duration	Done %			Refrences
Rivastigmine	Man	Female	Man	Female	medicine	placebo	3-6 mg	6-12 mg	52 week	medicine		placebo	[46]
	11	13	9	11	74.11 ±0.87	73.4± 0.9	3	21		87.5		100	
	80	107	-	-	75	-	2-12 mg		26 week	80		-	[47]
	345		187		74.3		1-4 mg	6-12 mg	26 week	80-81		75	[48]
							192	153					
	464		235		73.4		1-4 mg	6-12 mg	26 week	65	85	84	[49]
	243	243	239		50-85		1-4 mg	6-12 mg	26 week	86	67.48	87	[50]
							243	243					

Memantine	35	91	47	79	76		20 mg		28 week	72			[51]
	112	206	61	91	74.0 ± 7.4	73.3 ± 6.9	20 mg		24 week	85		91	[52]
Galantamine	287		-		70.2±9.6		16 mg	24 mg	156 week	27.9			[53]
							115	172					
	118	208	115	205	76.5 (7.77)		16 – 24 mg		6 month	79			[54]
Donepezil	35	40	39	65	73.2 ±7.39	75.1 ±7.75	10 mg		24 week	80		85.5	[55]
	7023	13451	-	-	82.2±6.3	-	3 – 10 mg		77 week	58.3		-	[56]
	107 118	164 155	123	151	71±0.5	72±0.5	5 mg	10 mg	30 week	88	84	80	[57]
Aducanumab	784	863	-		70.1±7.45		3-10 mg/kg		18 month	85.7	91.6	86.9	[58]
	65	60	17	23	72.6 ± 8.1	72.8 ± 7.2	1 – 10 mg/kg		54 week	-			[59]
	12	27	5	9	67.7	66.9	0.3 – 60 mg/kg		24 week	92.3			[60]

Table 2. Summary of Experimental Results for FDA-Approved AD Drugs Across Cognitive and Behavioral Assessment Scales

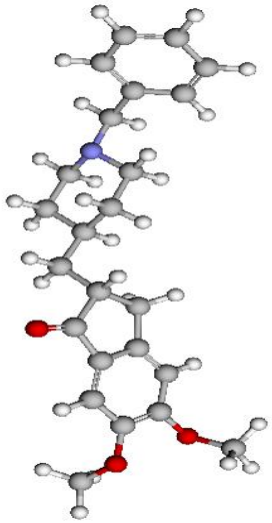
Medicine name	Refrences	ADAS-cog		CIBIC-plus	MMSE	PDS	ADCD/ADL	NPI
Rivastigmine	[61]	0.82±0.71		0.16±0.14	0.2±0.1	-1.14±1.1	–0.33±0.2	-
	[50]	1.17- -1.24		3.93 – 4.2	-	1.3- -2.9	-	-
	[47]	20.8		-	20.2	56.2	-	-
	[48]	– 2.3±0.62	– 3.4±0.54	-	-	-	-	-
	[49]	-3	-3.8	-	-	-	-	-
Memantine	[51]	-		4.5±1.12	- 0.5±2.40	-	- 3.1±6.79	0.5±15.76
	[52]	25.9 ± 10.4		4.12	18.6 ± 3.3	-	−1.99	−1.45
Galantamine	[53]	22.3 ± 7.9		-	-	-	-	-
	[54]	-		-	17.80 (4.14)	-	–1.0 (1.12)	–1.2 (0.83)
Donepezil	[55]	−3.56		3.68	1.29	-	2.142	-
Aducanumab	[58]	-0.588 - -0.583		-	-0.1 – 0.2	--	0.7	-
	[59]	-		-	24.2 ± 3.5	-	-	-
	[60]	20.7		-	21.3	-	-	-

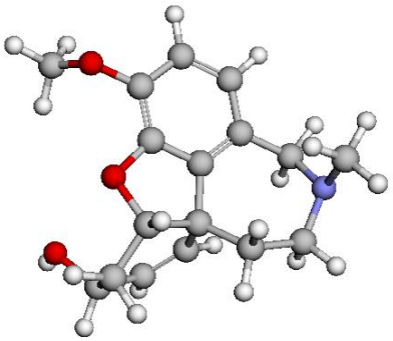
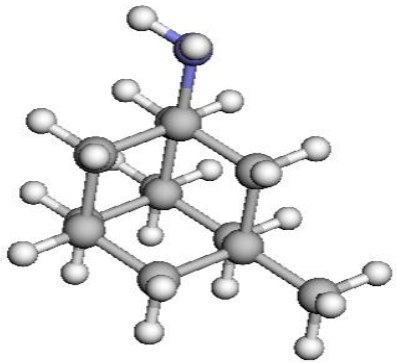
Table 3. Adverse events reported in clinical trials of FDA-approved drugs for AD

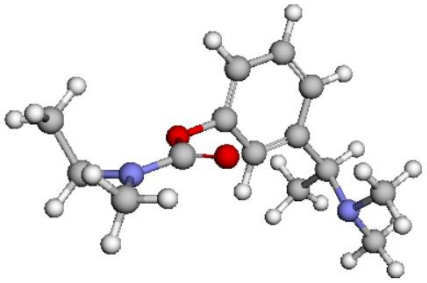
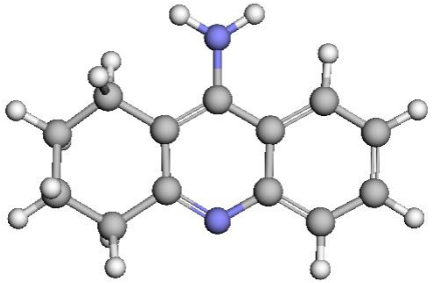
Medicine name	Refrences	Adverse events	Anorexia	Abdominal pain	Diarrhea	Dizziness	Headache	Urinary tract infection	Vomiting	Nausea	Death
Rivastigmine	[61]	-	8.3	4.1	-	8.3	8.3	-	12.5	16.6	-
	[50]	7.4 – 22.6	3 - 14	5 - 12	10 - 17	10 - 20	7 - 19	-	8 - 34	17 - 50	≤ 1
	[49]	8-29	-	-	-	-	-	-	-	-	≤ 1
Memantine	[51]	84	-	18	10	-	-	6	-	-	-
	[52]	8.8	-	-	-	5.3	5.7	-	-	-	-
Galantamine	[53]	72	-	-	-	12	-	12	10.7	17.3	-
	[54]	7	7	-	7	7	6	7	9	14	≤ 1
Donepezil	[57]	9 - 18	4 - 8	-	10 - 16	5 - 9	-	-	4 - 16	7 - 24	-
	[55]	9.2	-	-	5.3	-	10.7	-	-	8	2.7
Aducanumab	[58]	85.7 – 91.6	-	-	6.7 – 8.9	-	14.3 - 20.5	-	-	-	0 – 0.8
	[60]	54	-	-	13	-	21	10	-	-	0
	[59]	89.6	-	-	10.4	-	20	12.8	-	8	0

Description : All data is expressed in percentage terms

Table 4. Characteristics of FDA-approved drugs for AD (https://www.alzforum.org/)

Name	Synonyms	Chemical structure	FDA Status	Target Type	Therapy Type	Approved For	Side Effects
Aduhelm	Aducanumab BIIB037	Not Available	AD (Approved)	Amyloid-Related	Immunotherapy (passive)		-
Donepezil	Aricept™ Donepezil hydrochloride Eranz® E 2020		AD (Approved), Dementia with Lewy Bodies (Inactive), Down's Syndrome (Inactive), Parkinson's Disease Dementia (Inactive)	Cholinergic System	Small Molecule	AD, Dementia with Lewy Bodies (Japan)	Nausea, loss of appetite, diarrhea, insomnia, headaches, dizziness, orthostasis and nightmares

Galantamine	Razadyne™		AD (Approved)	Cholinergic System	Small Molecule	Mild to Moderate AD	Nausea, loss of appetite, diarrhea, insomnia, headaches, dizziness, orthostasis and nightmares
	Reminyl™						
	Nivalin®						
Leqembi	Lecanemab-irmb	Not Available	AD (Approved)	Amyloid-Related	Immunotherapy (passive)		-
	BAN2401						
	mAb158						
Memantine	Ebixa™		AD (Approved)	Other Neurotransmitters	Small Molecule	AD	Constipation, dizziness, and headache
	Namenda™						
	Axura®						
	Akatinol®						
	Memary®						

Rivastigmine	Exelon™ Rivastigmine tartrate Rivastach® Patch Prometax® SDZ ENA 713 MK-4305		AD (Approved), Parkinson's Disease Dementia (Approved)	Cholinergic System	Small Molecule	Mild to moderate AD and mild to moderate dementia related to Parkinson's disease	Nausea, loss of appetite, diarrhea, insomnia, headaches, dizziness, orthostasis and nightmares
Tacrine	Cognex™		AD (Approved 1993) Withdrawn (2013)	Cholinergic System	Small Molecule		Nausea, Vomiting, Loss of appetite, Diarrhoea, Clumsiness and also, Liver toxicity

The IC_{50} values of various acetylcholinesterase (AChE) inhibitors were analyzed and represented using a violin plot and a bar plot to illustrate their distribution and comparative inhibitory potency (Figure 3). The pIC50 value, the negative logarithm of the IC50, indicates that higher values correspond to greater potency. The violin plot shows the density of data points for each inhibitor: Donepezil showed moderate potency with some variability centered around a pIC50 of 5; galantamine had a broader range between 5 and 7, indicating higher potency variability; memantine had a narrow distribution around 5.5, showing consistent moderate potency; the new compound stood out with a concentrated distribution around 6.5, suggesting higher and more consistent potency; rivastigmine had consistent values around 5 with less variability; and tacrine had a narrow distribution around 5 with some outliers, indicating consistent potency. The bar graph provides detailed distributions: Donepezil-related compounds, such as quercetin and kaempferol, ranged from 50 to 100 in pIC50, indicating moderate potency; galantamine showed significant variability with values from 50 to nearly 200; memantine ranged from 60 to 80, indicating consistent moderate potency; the new compound showed high potency with some values reaching up to 200; rivastigmine ranged from 80 to 100, indicating consistent and relatively high potency; and tacrine ranged from 50 to 100, indicating moderate potency with less variability. Both plots indicate that the new compound has the highest inhibitory potency, while rivastigmine and memantine are shown to be reliable inhibitors with consistent values.

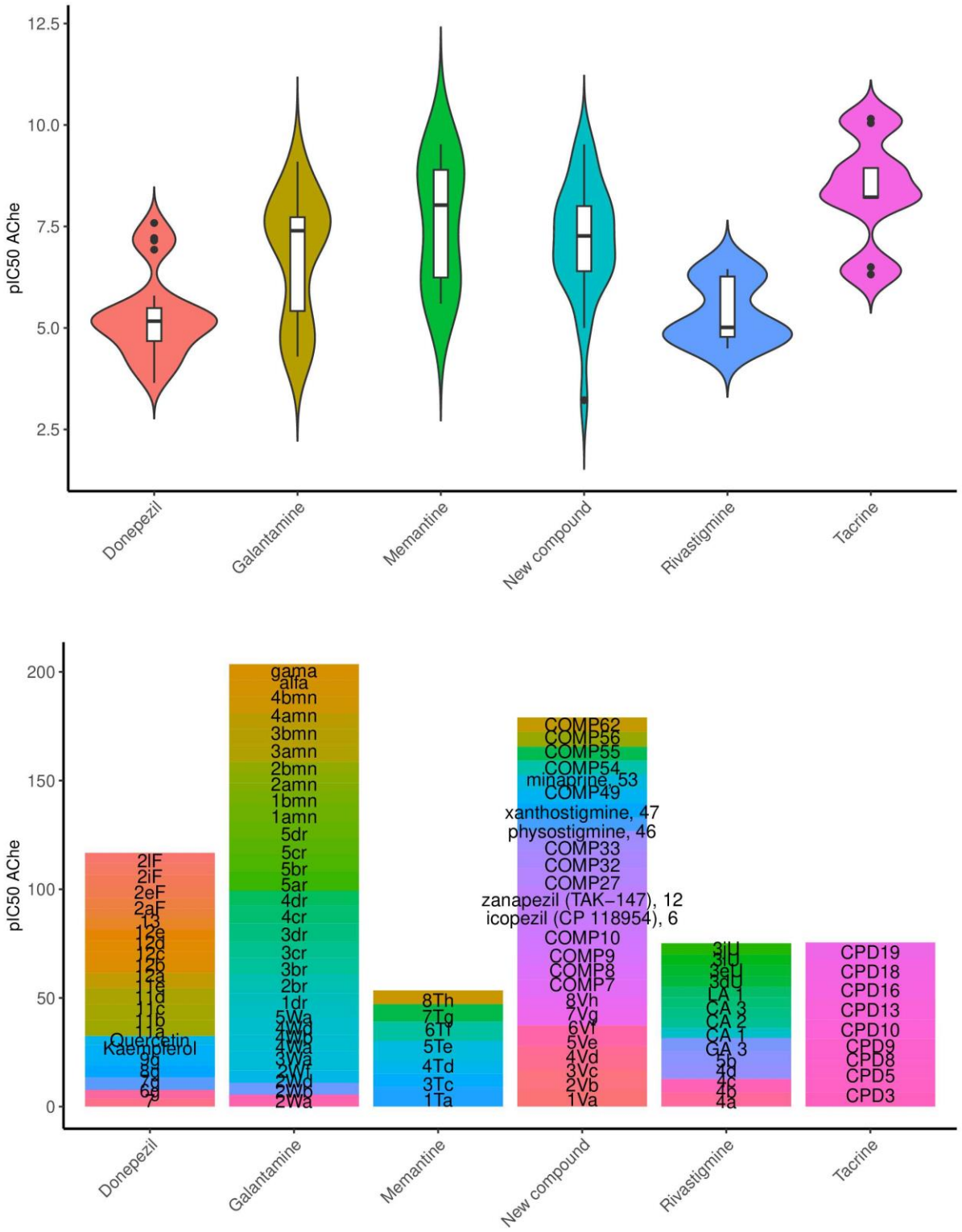
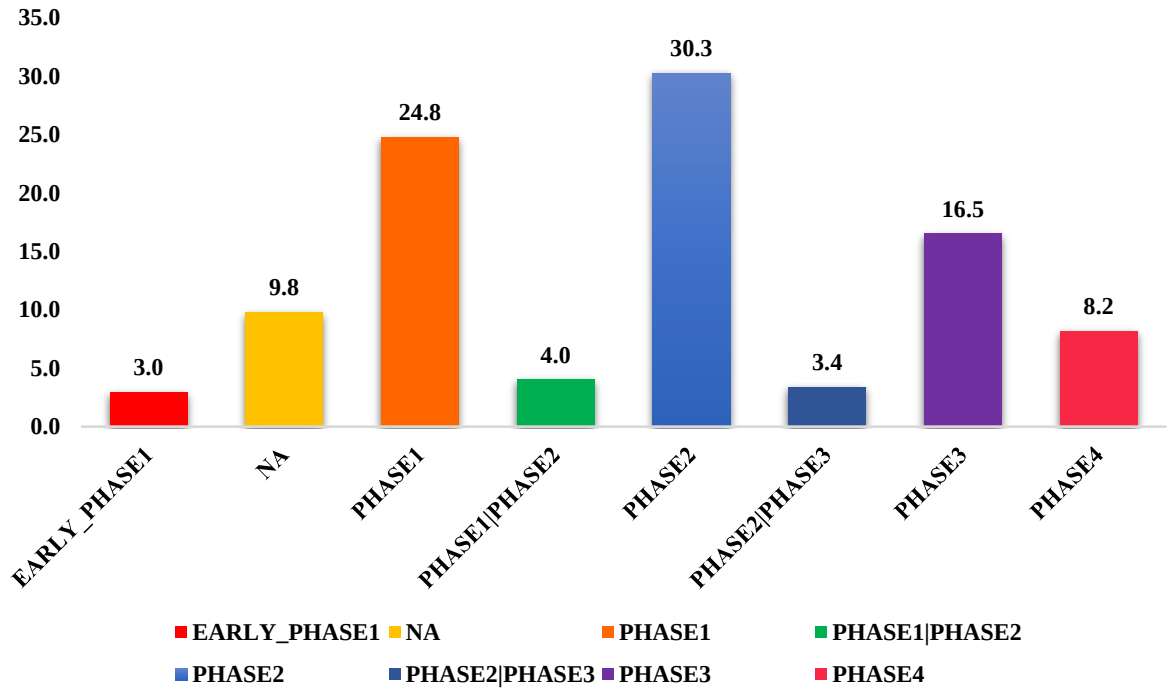


Figure 3. Violin plot and bar graph of the pIC50 values of several acetylcholinesterase (AChE) inhibitors, including donepezil, galantamine, memantine, a new compound, rivastigmine, and tacrine.

5. Challenge in AD drug discovery

The landscape of drug development, from initial clinical trials to eventual regulatory approval, reveals a pervasive challenge across multiple therapeutic areas worldwide. Drug discovery and development is a lengthy and expensive process, taking 10-15 years and costing $1-2 billion per drug. Despite rigorous preclinical work, around 90% of drug candidates fail in clinical trials, with even higher failure rates when considering preclinical stages[62]. As a result, approved drugs carry high prices, a necessary measure to offset the significant financial risks associated with numerous trial failures. The multifaceted etiology of AD and the escalating financial burden on healthcare systems underscore the urgent need to advance AD prevention and treatment modalities. At the time of the most recent assessment in June 2024, there were 1,513 ongoing clinical trials for AD reported on ClinicalTrials.gov (Figure 4), with a significant focus on drug therapies and a few on antibody therapies, but over 99% of small molecules have failed in AD trials[63]. Clinical trials for the treatment of AD are listed in the **Supplementary Table 1**.



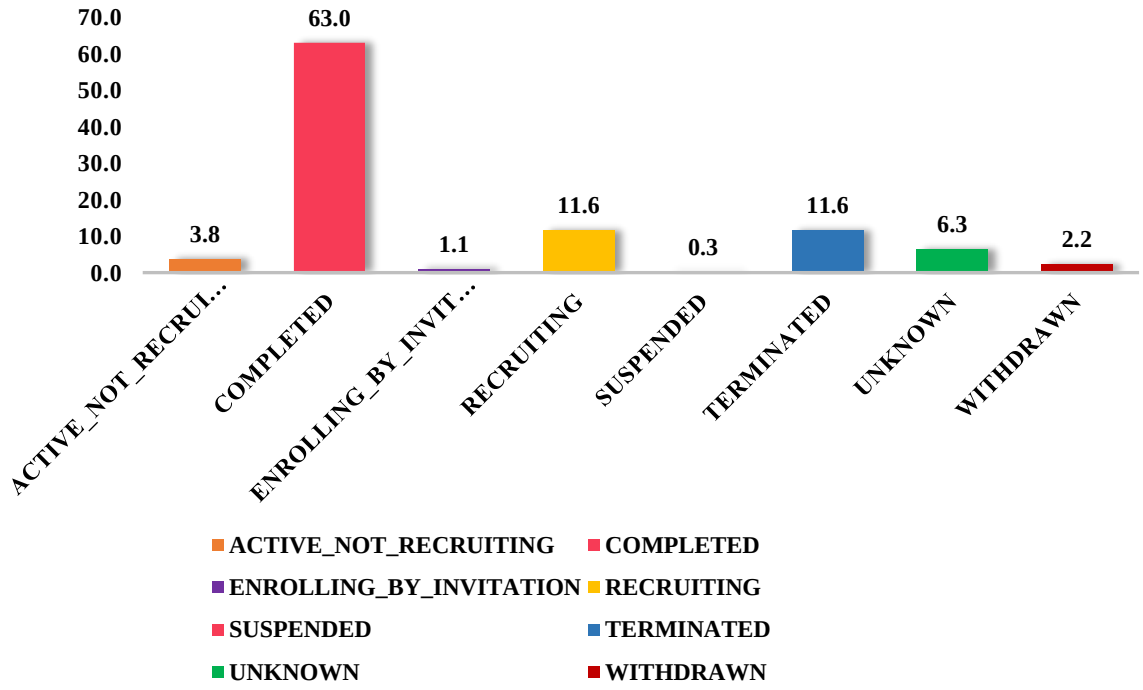


Figure 4. Distribution of AD clinical trials by phase and trial status. This figure illustrates the distribution of clinical trials across different phases of drug development, from preclinical to more advanced phases such as Phase 1, 2, 3, and 4. It also shows whether they are ongoing, completed, terminated or discontinued for various reasons.

Despite significant progress with monoclonal antibody-based interventions, the vast majority of small-molecule interventions (more than 99%) have failed in AD clinical trials[63], [64]. Therefore, it is of paramount importance to delve into the intricate genetic underpinnings of AD in order to identify novel therapeutic targets, as genetic predispositions contribute substantially, ranging from 58% to 79%, to the neuropathology of AD[63]. To date, genome-wide association studies (GWAS) have uncovered approximately 80 loci of significant genetic relevance to AD. Nevertheless, bridging the gap between human genetic discoveries and the realization of novel drug entities remains a daunting task, largely due to the preponderance of AD-associated loci located in non-coding genomic regions, the functional nuances of which remain largely unexplored[65], [66].

6. Overview of Genetic Research on AD

One major aim of medical research is to uncover the genetic and environmental factors responsible for diseases, including AD[67]. Advancements in microarray technology have enabled Genome-Wide Association Studies (GWAS) to link thousands of single nucleotide polymorphisms (SNPs) with disease risk. Large-scale projects like the International AD Project (IGAP) have conducted extensive GWAS on late-onset AD, involving thousands of patients. Two recent GWAS have significantly increased the sample sizes and identified more disease susceptibility loci. One study expanded the sample size to over 1.1 million, including new biobank and population-based dementia datasets. Another built on an earlier IGAP study, bringing the total sample size to 788,989. In total, the two GWAS studies uncovered 90 different variants at 75 loci associated with AD/dementia susceptibility, 42 of which were newly identified[68].

To date, AD/dementia GWAS have identified 101 independent AD-associated SNPs at 81 loci with genome-wide significance. The first gene associated with late-onset AD was APOE3, which is known to have isoforms that influence AD risk, with the APOE4 allele significantly increasing risk. Genetic linkage analysis, an early strategy, has mapped genes responsible for early-onset familial AD (EOAD) to chromosomes 21, 14, and 1. The analyses have revealed that individuals with Down syndrome, who have an extra chromosome 21, exhibit EOAD-like pathology. Genetic variations, combined with environmental factors, can alter gene expression in brain cells, leading to AD. The discovery of mutations in the APP, PSEN1, and PSEN2 genes led to the amyloid cascade hypothesis and had a major impact on AD research. Although rare, mutations in these genes have large effects. In addition, GWAS have identified associations between AD risk and rare variants in genes such as TREM2, SORL1, and ABCA7. Recent studies have also found AD risk signals in novel genes such as ABCA1 and ATP8B4, and suggestive associations with variants in RIN3, CLU, ZCWPW1, and ACE. Variants in APOE3, such as V236E and R136S, have shown potential to reduce AD pathology and delay disease onset in individuals with PSEN1 mutations[67], [68], [69], [70], [71].

Genetic variations, combined with environmental factors, can alter gene expression in brain cells, leading to AD. High-throughput microarray and RNA-sequencing (RNA-Seq) technologies allow detailed examination of these changes, helping to identify potential therapeutic targets. However, the complexity of data necessitates the use of ML for effective analysis. Next-generation sequencing (NGS) enables comprehensive and accurate sequencing

of the human genome. Whole-exome sequencing (WES) and whole-genome sequencing (WGS) provide extensive DNA data, helping to identify rare variants associated with AD risk. NGS has uncovered new mutant genes and susceptibility loci missed by GWAS, such as NOTCH3 and SORL1[67], [71], [72].

7. AI application in AD

AI and ML technologies are applied at three pivotal stages of early drug discovery: target identification, lead generation and optimization, and preclinical development. In the realm of target discovery, AI techniques amalgamate diverse datasets to discern patterns, thereby elucidating the molecular mechanisms of diseases and drug actions. For lead generation and optimization, ML algorithms enhance scoring functions and quantitative structure–activity relationship (QSAR) models within virtual screening frameworks, facilitating the automation and refinement of *de novo* drug design. During preclinical development, ML approaches create predictive models for physicochemical properties by processing substantial volumes of chemical data, further refining absorption, distribution, metabolism, and excretion-toxicity (ADME-T) profiles[63], [73], [74].

7.1. AI in AD diagnosis

AD can be diagnosed based on clinical symptoms; however, there is currently no universally accepted clinical standard for diagnosing AD in living individuals. A definitive diagnosis is made postmortem by identifying neurofibrillary tangles (NFT) or diffuse amyloid deposition, which are closely associated with the disease. Research indicates that the onset of the neuropathological hallmarks of AD, such as NFTs and abnormal amyloid plaques, begins years before the onset of clinical symptoms. Therefore, the identification of biomarkers and the use of imaging techniques to detect early signs in high-risk individuals is critical. In this context, beta-amyloid and tau levels in cerebrospinal fluid (CSF) and changes in brain volume are detectable through imaging. Neuroimaging is critical in identifying early diagnostic indicators of AD, facilitating early diagnosis and intervention. The most common imaging modalities used to diagnose neurodegenerative diseases include magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET). However, rapid advances in neuroimaging technology have created challenges in managing and interpreting

large amounts of brain imaging data. To address these challenges, computer-based algorithms, particularly those based on AI, are increasingly being used for integrative analysis[75], [76].

One study developed an ML algorithm to classify AD by examining abnormal hippocampal functional connectivity. The study included 119 participants aged 60-85 years who underwent functional MRI scans and were classified into AD, mild cognitive impairment (MCI), or normal control (NC) groups. The support vector regression (SVR) model used achieved accuracies of 82%, 81%, and 81 % in distinguishing AD from NC, MCI from NC, and AD from MCI, respectively[77]. In addition, deep learning techniques, particularly convolutional neural networks (CNNs), have been shown to be highly effective in detecting Alzheimer's disease (AD); in one study, CNN-based models achieved outstanding performance, with test and validation accuracies of 96% and 99%, respectively, in identifying AD from MRI scans[75], [78]. In another study, researchers introduced a densely connected convolutional neural network (CAM-CNN) with a connection-wise attenuation mechanism to improve the accuracy of AD diagnosis using MRI brain scans. This approach achieved accuracies of 97% for identifying mild AD patients, 88% for MCI converters, and 79% for stable MCI subjects compared to healthy controls[79]. In other studies, a multimodal deep neural network was created using structural MRI and FDG-PET images for early diagnosis of AD. This method showed an accuracy of 94% in classifying individuals with probable AD, an accuracy of 86% in identifying MCI individuals likely to convert to AD within 1 to 3 years, and an accuracy of 86 % in classifying non-demented controls[80]. Also, Yu et al. proposed the Multidirectional Perception-Generative Adversarial Networks (MP-GAN), which uses MRI images to identify key features indicative of AD. This model stands out for its ability to highlight subtle lesions through image transformations, proving effective in experiments using the AD Neuroimaging Initiative (ADNI) dataset[81]. El-Sappagh et al. proposed a two-layer explainable ML using data from 11 modalities, including genetics and neuropsychological scores. Their model achieved high accuracy in multi-class classification and showed potential for early MCI to AD prediction[82].

7.2. AI in Drug Discovery

The advent of artificial intelligence (AI) methodologies presents a transformative potential for the drug discovery and development process, spanning from foundational research to pre-clinical and clinical phases. Compared to traditional biological experiments, AI-based models

have shown greater speed and efficacy by utilizing extensive biomedical datasets[73], [83], [84]. These AI methodologies encompass models based on ML, deep learning, and network algorithms. ML, a branch of AI, is a set of data analysis techniques designed to create predictive models by learning from data. These models improve their predictive accuracy over time through experience. Deep learning (DL), a subset of ML, employs methods capable of understanding the relationships between inputs and outputs by modeling complex, non-linear interactions into more abstract, higher-level representations[85], [86].

ML encompasses the creation and application of algorithms that determine actions based on data analysis and its properties, rather than being explicitly programmed for specific outputs. These algorithms are typically adaptive, enhancing their performance as they are exposed to more data. ML algorithms are generally categorized into four types: supervised learning, unsupervised learning, semi-supervised learning, and reinforcement learning. Each type employs different algorithms to accomplish tasks such as classification or clustering. However, successful AI implementation involves more than just training a model. A comprehensive AI workflow includes several steps: problem formulation, data preparation, feature extraction, selection of training and testing datasets, model development, model training and performance testing (cross-validation), and application and refinement of the model on testing datasets.[73], [87], [88]

7.3. AI in AD omics data analysis

In the field of data analysis, traditional statistical modeling has long been the method of choice for interpreting large data sets. In recent years, however, AI has become increasingly prominent in various disciplines. This shift is largely due to the transformation of data from traditional structured formats to more complex forms such as unstructured, semi-structured, and heterogeneous data with varying characteristics. In addition, the need for deeper and more accurate insights into biological mechanisms has raised the bar for omics analysis[89], [90].

To develop precision medicine and personalized treatments for AD, it is crucial to integrate various multiomic datasets such as the genome, transcriptome (including single-cell transcriptomics), proteome, metabolome, phenome, radiome, and human interactome (protein-protein interactions). Leveraging these datasets, researchers can create advanced AI and *in silico* models, encompassing ML and network medicine approaches, as well as cell-type-specific models for microglia, astrocytes, and neurons. These models have the potential to

enhance patient stratification, pinpoint targets for drug discovery or repurposing, and tailor treatments for AD and other complex brain disorders. So, high-throughput experimental data databases are essential for developing AI-driven solutions that can effectively identify drug targets, elucidate disease pathobiology, and understand the mechanisms of drug actions[91].

7.4. AI in AD treatment

Computer-aided drug design (CADD) has become an essential part of the drug discovery and development landscape. Its introduction has dramatically sped up the process, cutting down the time needed for experimental work. With the rise of computer-based strategies, key concepts such as structure-based drug design (SBDD) like molecular docking and dynamics, ligand-based drug design (LBDD) including quantitative structure-activity relationships (QSAR) and pharmacophore modeling, and virtual screening (VS) have become integral to the field (Figure 5). The combination of CADD and ML has opened up numerous possibilities in drug discovery. These approaches have been particularly effective in reducing costs, saving time, filtering out ineffective molecules early on, and decreasing the likelihood of failure in the final stages of drug development[92], [93], [94], [95].

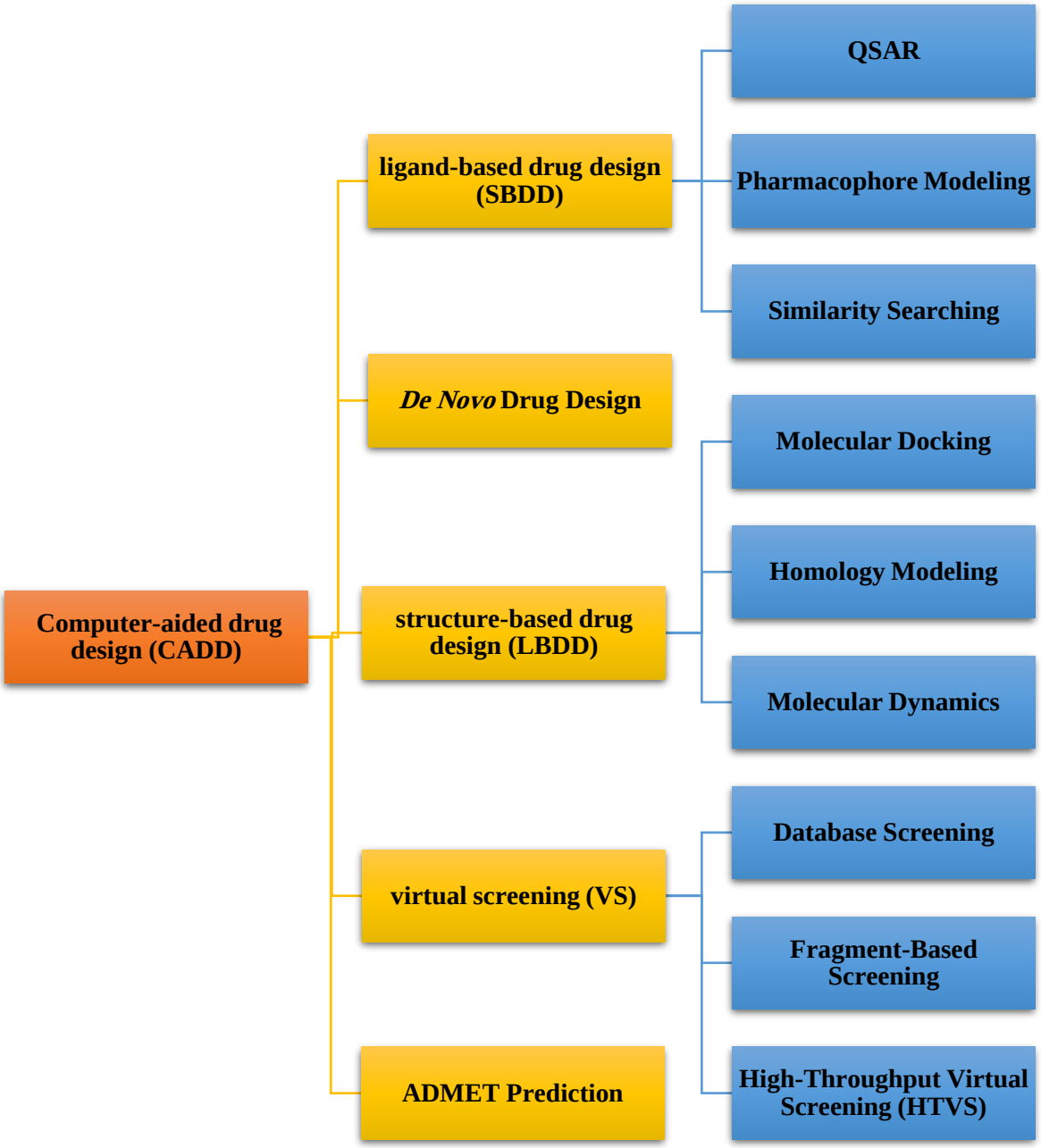


Figure 5. Computer-based drug design strategies, including structure-based drug design (SBDD), ligand-based drug design (LBDD), *De Novo* Drug Design, virtual screening (VS), and ADMET Prediction.

7.4.1 AI in *de novo* drug design

De novo drug design (DNDD) is about designing new chemical entities (NCEs) from scratch, using computational algorithms. The term "de novo" means "from the beginning," highlighting

that this approach generates new molecular entities without any pre-existing templates. The inputs for this process come from various ligand representations, including SMILES (Simplified Molecular Input Line Entry Systems), molecular graphs, molecular fingerprints, and 3D structures. The benefits of DNDD are substantial: it allows for exploring a vast chemical space, creating compounds that can become novel intellectual property, developing potentially groundbreaking therapies, and doing all this in a cost- and time-efficient manner. Recently, the scope of chemical search space has significantly expanded thanks to AI generative models. These include techniques like recurrent neural networks, encoder-decoder models, reinforcement learning, generative adversarial networks, flow-based models, and hybrid models. These advancements in AI-based *de novo* drug design are making drug development faster and more efficient, though there are still some challenges to overcome[63], [96].

7.4.1.1 Structure-based *de novo* drug design

When it comes to structure-based *de novo* drug design, everything starts with identifying the receptor's active site. This area of the receptor is crucial since its shape, physical, and chemical properties dictate how well a ligand can bind to it. By analyzing the active site, scientists determine the shape constraints and the types of non-covalent interactions, such as hydrogen bonds, electrostatic forces, and hydrophobic interactions, that a ligand can form. These interactions help create specific sites where ligands can bind, which is essential for reducing the vast number of potential molecular structures and improving selectivity. Various methods are used to define these interaction sites. For example, HSITE is a rule-based method that focuses on hydrogen-bond donors and acceptors to map out hydrogen-bonding regions. Other methods like LUDI and PRO_LIGAND also consider hydrophobic interaction sites, while HIPPO includes covalent and metal ion bond interaction sites. Some approaches use grids, generating a series of points within the active site and calculating interaction energies for each point. The multiple-copy simultaneous search (MCSS) method docks functional groups randomly within the active site to find the most energetically favorable positions, discarding those that don't meet a certain energy threshold[97], [98].

AlphaFold 2 (AF2) has revolutionized structure-based drug discovery by providing accurate protein structure predictions, especially for proteins without known structures. Researchers have found that AF2 can enhance virtual screening and free energy calculations, though its

binding sites often resemble apo structures more than holo structures. Efforts to refine AF2 models have shown promise in improving their utility. Studies have demonstrated that AF2 structures can perform better than homology models in some cases, and they can predict binding free energies with similar accuracy to crystal structures. Additionally, tools like the ProBiS-Fold web server have used AF2 to identify thousands of new, highly druggable binding sites, highlighting AF2's potential to unlock numerous new targets for drug discovery[99], [100].

7.4.1.2. Ligand-based *de novo* drug design

Early methods of ligand-based *de novo* drug design, like LeapFrog and SPROUT, marked significant advancements in generating new molecules. LeapFrog combined a genetic algorithm with a 3D molecular field scoring model (3D-CoMFA), starting from known ligands to create novel compounds. SPROUT, on the other hand, utilized atomic constraints derived from existing drugs or ligands, with or without 3D receptor coordinates. These early techniques focused on simple rules to ensure chemical validity, primarily considering atom valences and bond orders but often neglecting chemical feasibility and drug-likeness. SPROUT was among the first to address synthetic feasibility with a specific algorithm called Computer Assisted Estimation of Synthetic Accessibility[101].

However, ligand-based *de novo* design has its limitations, mainly due to the dependency on existing target-specific ligand datasets and the lack of pharmacological property predictions. To overcome these challenges, recent innovations have emerged. One such approach is the RELATION model, an encoder-decoder-based generative model that extracts 3D binding pocket features from protein-ligand complexes to generate effective molecules, showing high efficacy in AKT1 and CDK2 targets. Similarly, the Sakurai group introduced DeepTarget, an AI model that uses protein amino acid sequences to guide molecule generation, achieving impressive results with DRD2 and PARP1 datasets. Designing molecules with high drug potential involves tackling challenges like drug-likeness and logP metrics. To address this, researchers proposed an iterative refinement framework using a graph-based molecular quality assessment model (QADD). This model incorporates a molecular quality assessment module into a graph neural networks (GNN) model to score drug potentials and employs a multi-objective deep reinforcement learning algorithm to optimize multiple molecular properties. The

generated molecules demonstrated superior validity, success rates, and novelty compared to the RNN-based REINVENT model[63], [102], [103].

7.4.2. AI virtual screening in AD

High-Throughput Screening (HTS) and Virtual Screening (VS) are two essential techniques in drug discovery. HTS involves the rapid testing of large numbers of compounds for biological or biochemical activity. This process uses automated equipment and miniaturized assays to process thousands of samples simultaneously, making it a go-to method in the early stages of drug discovery. However, HTS can be time-consuming and resource-intensive, with a low number of successful hits. To enhance the efficiency of HTS, researchers often use VS, a computational technique that identifies potential drug candidates by predicting their interactions with drug targets, such as protein receptors or enzymes, without physical experimentation; however, VS is not a replacement for HTS[104].

The first step in VS is the creation of a compound database for the screening process. This often involves pulling large amounts of data from public chemogenomics libraries such as ChEMBL, PubChem, or ZINC, each of which contains tens of millions of compounds with detailed annotations about their structure and known targets. Then the VS begins, either as Structure-Based Virtual Screening (SBVS) or Ligand-Based Virtual Screening (LBVS), or sometimes a mixture of the two. SBVS examines the structures of the ligand and the target binding site to predict how likely the ligand is to bind. This often involves docking, where compounds are "placed" in the target binding site and scored for their binding probability based on predefined metrics. LBVS, on the other hand, doesn't need structural information and instead relies on the molecular and chemical properties of known and tested compounds[105].

ML has become a useful tool in virtual screening, significantly increasing the yield of potential drugs by sifting through millions of compounds *in silico*. Key ML algorithms used in this context include Bayesian methods, support vector machines (SVM), supervised learning, dimensionality reduction, artificial neural networks (ANN), and ensemble algorithms. Bayesian learning algorithms, for example, can represent input data as feature vectors and plot them in a space of the same dimensionality. These algorithms have been particularly effective in studying the biological activities of small molecules and prioritizing them for experimental screening for diseases such as AD and Parkinson's (PD). A Bayesian ML virtual screen even identified several glycogen synthase kinase-3β (GSK3β) inhibitors from a large library of

FDA-approved drugs and clinical candidates. Google DeepMind's AlphaFold has revolutionized the field by predicting 3D protein structures from amino acid sequences, streamlining the determination of target protein structures that are critical to drug design[105], [106].

In addition, AI-based scoring capabilities have been developed to improve the accuracy of molecular docking. For example, Lu et al. introduced ΔvinaXGB, an AI-based scoring function that incorporates parameters such as water and ligand stability along with protein-ligand interaction terms. This model demonstrated robust performance on the CASF-2016 benchmark, outperforming traditional docking strategies such as AutoDock Vina[63].

7.4.3 AI Pharmacokinetic/Pharmacodynamic Evaluation in AD

In recent decades, understanding the properties associated with absorption, distribution, metabolism, excretion, and toxicity (ADMET) has become a key focus in drug discovery and development. Pharmacokinetics is the study of how drug concentrations change over time in a biological system. This field encompasses the processes of absorption, distribution, metabolism, and excretion, collectively known as ADME. A drug must exhibit favorable pharmacokinetic behavior in order to move beyond the discovery phase and into further stages of development. The pharmacokinetics of a drug are influenced by several factors, including its physicochemical properties, intrinsic clearance, volume of distribution, and interactions with body tissues and fluids. After a drug is absorbed into the bloodstream, it reaches peak concentration, is distributed throughout the body, is metabolized primarily by the liver, and is ultimately excreted primarily by the kidneys. Transporter proteins, including solute transporters and ATP-binding cassette transporters, play a critical role in these processes. Key pharmacokinetic parameters include half-life ($t_{½}$), apparent volume of distribution (Vd), elimination rate constant (K_e), maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the concentration-time curve (AUC), and clearance (Cl). These parameters may vary depending on the method of drug administration[107], [108], [109]

The high failure rate of clinical trials in AD has put pressure on the pharmaceutical industry to improve the ADMET properties of drug candidates, especially for brain penetration. Since *in vivo* and *in vitro* evaluations are expensive and time-consuming, AI-based models have become essential for estimating these properties. For example, a substructure pattern recognition model

using support vector machines (SVM) was developed to predict BBB penetration, achieving an impressive 98.4% accuracy on test sets. Another AI approach, a light gradient boosting machine (LightGBM) model, was trained on thousands of BBB-permeable and non-permeable molecules and achieved 89% accuracy during cross-validation and 90% accuracy on an external validation set of CNS compounds. These advances in AI have led to several new models for predicting BBB penetration and other ADMET properties, demonstrating their potential in early drug discovery[110].

Overall, researchers have made significant strides in drug development by using AI tools, especially in tackling AD and related dementias (ADRD). So far, there are 158 drug candidates driven by AI that are currently in the discovery or preclinical stages for various diseases[83].

8. Public AD-related databases

Using AI for AD and other neurological research requires vast datasets, consisting of numerous entries with a wide range of clinical and biological variables. These datasets help develop innovative algorithms by analyzing the disease's features. Over the past two decades, there has been significant growth in open data-sharing initiatives in neurodegenerative disease research, particularly for AD[85].

Several key resources have emerged to support this data-sharing:

- The AD Genetics Consortium (ADGC) (http://www.adgenetics.org/)
- The AD Sequencing Project (ADSP) (https://adsp.niagads.org/)
- ADNI (https://adni.loni.usc.edu/)
- AlzGene (http://www.alzgene.org/)
- Dementias Platform UK (DPUK) (https://portal.dementiasplatform.uk/)
- Genetics of AD Data Storage Site (NIAGADS) (http://www.niagads.org/)
- Global Alzheimer’s Association Interactive Network (GAAIN) (https://www.gaain.org/)
- National Centralized Repository for AD and Related Dementias (NCRAD) (https://ncrad.iu.edu/)

These public databases collect a wide range of data, including biological specimens, clinical and cognitive test results, lifestyle information, neuroimages, genetic data, and CSF and blood biomarkers from individuals who are normal, cognitively impaired, or demented. This wealth

of data is essential for applying advanced ML algorithms. Moreover, the National Alzheimer's Coordinating Center (NACC) (https://naccdata.org/) has developed a comprehensive relational database for AD research, using standardized clinical and neuropathological data. DementiaBank (https://dementia.talkbank.org/), a part of TalkBank, provides language data related to dementia, including audio files and text transcriptions from verbal tasks like the Pitt corpus[85], [111].

High-throughput experimental data from specialized databases are crucial for creating AI-based solutions to identify new drug targets, enhance understanding of disease biology, and uncover drug action mechanisms for AD treatment. For example, high-throughput DNA/RNA sequencing projects like the ADSP and ADNI have generated extensive genomic data. Key databases such as NIAGADS have accumulated vast genetic and genomic datasets, while initiatives like the Accelerating Medicines Partnership® Program for AD (AMP® AD) focus on identifying therapeutic targets and biomarkers. Databases like DrugBank and DrugCentral provide comprehensive drug-target information, supporting AI-driven drug discovery efforts. The AlzGPS platform integrates multi-omics and clinical data, helping researchers evaluate thousands of drugs and develop treatment strategies for AD. The ADNI is one of the most frequently cited datasets, offering a comprehensive longitudinal dataset with genomics, images, clinical data, and biospecimens. The Religious Orders Study/Memory and Aging Project (ROSMAP) is another valuable multi-omic longitudinal dataset that includes genomics, transcriptomics, methylomics, proteomics, and metabolomics. The Gene Expression Omnibus is also a notable source for gene expression profiling[112], [113], [114], [115], [116].

9. Target identification for AD by AI

ML algorithms are increasingly crucial for analyzing large genetic datasets, aiding in AD diagnosis, prognosis, and the study of gene interactions. By integrating various omics datasets (genome, transcriptome, proteome, metabolome, and more), AI approaches can develop precision medicine and personalized treatments for AD. By examining changes in gene expression within brain cells, researchers can identify key genes and pathways involved in AD, which could serve as targets for new treatments. High-throughput techniques like microarrays and RNA sequencing (RNA-Seq) provide a detailed view of the cell or tissue transcriptome, but the data's complexity requires advanced analysis methods. In 2011, Kong and colleagues developed two unsupervised ML algorithms, ICA and NMF, to analyze gene expression in the

hippocampus of both AD patients and control subjects. They found that many genes related to metal metabolism and inflammation were significantly altered in AD patients. Scheubert used a combination of genetic algorithms and support vector machines (GA/SVM) to efficiently identify genes linked to AD, discovering new candidate biomarkers such as LOC642711 and LY6H. Panigrahi and team took an integrative systems biology approach to uncover genes and biological processes related to AD and aging, using supervised learning software and self-organizing maps to analyze microarray data from the hippocampus, frontal lobe, and blood mononuclear cells of AD patients. They identified ten major classes of transcription factors and unique miRNA targets as key regulatory processes in AD. Other researchers, like Nishiwaki and Miao, have used methods like the random forest algorithm and two-stage classifiers to find additional AD-related genes. Li et al. explored gene expression changes in both blood and brain tissues, discovering that over 77% of genes exhibited consistent regulation across different tissues and disease states. They used SVM, random forest, and logistic ridge regression (RR) models to highlight pathways like mitochondrial dysfunction and NF-kappa B signaling as crucial in AD pathogenesis. Armananzas proposed a method to integrate gene expression data and sequence predictions with ML, identifying previously unreported microRNAs linked to AD, such as miR-106a and miR-504. ML has significantly advanced the early stages of drug discovery for AD by identifying and characterizing targets. For example, the Cordax method predicts amyloid core sequences using structural data, helping understand amyloid fibrils and identify potential drug targets. The HENA dataset combines various data types to predict AD-associated genes using a graph convolutional network (GCN). Network-based Bayesian approaches and projects like AI4AD use AI to analyze genetic, imaging, and clinical data, identifying new targets and biomarkers for AD[67], [117], [118], [119], [120].

10. Comparative Advantages of AI in Drug Design for AD Over Computational Approaches

Recent developments in AI have transformed the field of drug discovery for complex diseases such as AD. Traditional drug design methods have often been slow, expensive, and with limited clinical success. AI offers a more efficient alternative by processing large datasets from genomics, proteomics, and electronic health records to identify potential drug targets, repurpose existing drugs, and predict therapeutic outcomes with higher accuracy.[121]

10.1. AI-Driven Drug Development

The collaboration between Exscientia and Sumitomo Dainippon Pharma has resulted in one of the first AI-based drug discovery outcomes: DSP-0038, the first AI-designed molecule to enter Phase 1 clinical trials for the treatment of Alzheimer's disease psychosis. This molecule is designed to act as a dual 5-HT1A receptor agonist and 5-HT2A receptor antagonist. Such dual-target approaches are often difficult to achieve in conventional drug discovery due to challenges with selectivity and off-target effects. The trial will assess DSP-0038’s potential in mitigating behavioral and psychological symptoms of dementia (BPSD), such as agitation, aggression, anxiety, and depression, which are common but difficult-to-treat symptoms in AD.[122]

10.2. Predicting Blood-Brain Barrier Permeability

Crossing the blood-brain barrier (BBB) is a critical challenge in the development of drugs for neurodegenerative diseases such as Alzheimer's disease. AI models such as MegaMolBART have been developed to predict BBB permeability using molecular structures encoded as SMILES representations. Pre-training the model on the ZINC-15 dataset significantly improved its predictive performance. Unlike traditional physicochemical methods, these AI-based approaches offer greater flexibility and computational efficiency, enabling faster and more accurate identification of brain-penetrating drug candidates.[123]

10.3. AI in Drug Repurposing

AI is also proving effective in repurposing existing drugs for Alzheimer's disease. A recent study using ChatGPT identified several drugs, including metformin, simvastatin and losartan, as candidates associated with a reduced risk of Alzheimer's disease. Repurposing approved drugs for other indications accelerates the therapeutic development process, reducing the time and cost of bringing treatments to patients.[124]

10.4. Network-based approaches and multi-omics data integration

AI-powered network analysis has uncovered new therapeutic pathways in Alzheimer's disease by identifying Alzheimer's risk genes (ARGs) from multi-omics datasets. In one study, AI models integrated gene expression and regulatory data with Bayesian frameworks, revealing

enriched druggable targets in AD pathways. Drugs such as pioglitazone and carvedilol emerged as promising candidates. Pioglitazone, traditionally used for type 2 diabetes, was shown to reduce amyloid-β levels, while carvedilol, a beta-blocker for hypertension, improved cognitive function in animal models of AD by reducing beta-amyloid accumulation.[117]

10.5. Toward a Paradigm Shift in AD Treatment

AI-driven drug discovery has led to significant advances by optimizing candidate selection, predicting BBB permeability, and facilitating drug repurposing. In contrast to traditional methods that have struggled to develop highly effective AD therapies, AI has the potential to improve the efficiency and precision of drug development. Given that computationally designed drugs have had limited success in fully restoring cognitive function in AD patients, AI-designed drugs such as DSP-0038 could bring us closer to effective treatments for this challenging disease.

11. Limitations of AI in AD Diagnosis and Treatment

ML has revolutionized AD diagnosis and treatment. However, predicting the best targets for new treatments remains complex due to the lack of well-defined "ideal" targets. The data used for training ML models may not be sufficient to provide precise answers, and this challenge is compounded by the inherent limitations of the technology[125].

ML has shown great potential in clinical drug therapy, helping physicians and pharmacists make informed decisions about drug regimens, adverse reactions, and treatment outcomes. Research in this field relies heavily on hospital electronic medical records, genomics databases, and drug interaction databases. Despite advancements, challenges remain, such as the lack of standardized patient information entry, effective data quality control, and issues with data silos in databases. The quality and quantity of training data are crucial, but variations in AD patient examinations and data formats, along with inaccuracies like omissions and misdiagnoses, pose significant obstacles. Furthermore, a substantial volume of case data is necessary for training, but there are no standardized criteria for determining the required quantity and quality of data[125], [126], [127], [128].

While ML excels at data processing, it presents technical challenges. Many models function as black boxes, making it difficult for users to understand their internal workings and address errors. The diversity of ML methods complicates the selection of the most appropriate approach for specific clinical issues, requiring interdisciplinary communication and collaboration. The field's cross-disciplinary nature demands expertise in computer science, linear algebra, probability theory, and mathematical statistics, creating a barrier to widespread adoption. Developing user-friendly modeling tools for healthcare professionals could help mitigate this issue[129].

12. Ethical and Legal Issues

Ethical and legal considerations are crucial in the application of ML to AD. The use of substantial clinical and imaging data raises privacy and security concerns, necessitating informed consent for data collection, transmission, and storage. Data anonymization is essential, and patients should have the right to anonymize their data, especially for profit-driven uses. ML models are not infallible and can lead to misdiagnosis or treatment errors, requiring clear guidelines for legal responsibility. As ML tools become integral to clinical decision-making, ensuring data security and privacy is paramount. The development and application of ML in clinical settings must address these explicit ethical challenges[130].

13. Challenges in the AI-Driven Drug Discovery for AD

While AI has shown great promise in accelerating drug discovery for AD, several challenges remain that need to be addressed to fully realize its potential:

13.1. Lack of Understanding of Disease Mechanisms

A deeper understanding of the complex pathophysiology of AD is crucial for developing effective therapies. AI can help address this gap by analyzing large datasets from electronic health records and multi-omics profiles to provide insights that can guide therapeutic development[121].

13.2. High Failure Rates in Clinical Trials

The high failure rate of clinical trials in AD underscores the need for more accurate predictive models and better patient selection criteria. AI can optimize clinical trial design by identifying the most promising drug candidates, predicting drug-target interactions, and selecting patients most likely to benefit from the intervention[131].

13.3. Interpretability of AI Models

As AI becomes more widely adopted in drug discovery, the interpretability of these models becomes increasingly important. Researchers are working on developing explainable AI techniques that can provide insights into the decision-making process of these models, making them more transparent and trustworthy[63].

13.4. Collaboration and Data Sharing

Successful application of AI in drug discovery requires collaboration among researchers from various disciplines, including neurology, genetics, and data science. Additionally, open data sharing is crucial for training robust AI models. Initiatives like the ADNI have demonstrated the value of data sharing in accelerating research[121].

13.5. Ethical Considerations

As AI becomes more prevalent in healthcare, it is important to address ethical concerns such as data privacy, algorithmic bias, and the potential for job displacement. Establishing clear guidelines and regulations will be crucial for ensuring that AI is developed and deployed responsibly[131].

14. Future Directions in AI-Driven Drug Discovery for AD

Despite these challenges, the future of AI-driven drug discovery for AD looks promising. As AI technologies continue to evolve and more data becomes available, researchers are likely to make significant strides in understanding the disease mechanisms and developing effective therapies. Some key areas of focus include:

- Integrating multi-omics data with AI techniques to enhance our understanding of AD pathophysiology and facilitate precision medicine strategies[63], [121].
- Leveraging AI for drug repurposing to identify new uses for existing drugs, which can expedite the drug development process[63], [132].

- Applying AI to optimize clinical trial design and patient selection criteria to improve the success rate of clinical trials[131].
- Developing explainable AI techniques to make AI models more transparent and trustworthy[63].
- Fostering collaboration and data sharing among researchers to accelerate the pace of discovery[121], [131].

15. Conclusions

AI/ML technology holds great potential to advance drug discovery and clinical trials for AD. As high-quality databases are created and new algorithms are developed, collaborative efforts between clinical and computer researchers will likely expand ML applications in clinical drug therapy research. Utilizing sophisticated ML algorithms and tools can significantly improve the effectiveness of clinical prediction models in practice, enhancing diagnostic and treatment efficiency and enabling intelligent, personalized therapeutic decision-making.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Mohammd Hossein Ebrahim Abadi: Conceptualization, Writing – Original Draft, Investigation; **Ali-Reza Manavi Amin:** Writing – Review & Editing, Data Curation; **Yahya Sefidbakht:** Conceptualization, Supervision, Project Administration, Resources, Writing – Review & Editing; **Maryam Haghshenas:** Visualization, Data Curation, Writing – Review & Editing; **Moslem Afrashteh:** Methodology, Software, Data Curation; **Sina Mozaffari-Jovin:** Validation, Writing – Review & Editing; **Vladimir N. Uversky:** Review & Editing, Final Approval.

References

[1] Kumar A, Jaskirat Sidhu, Amandeep Goyal, and Jack W. Tsao, “Alzheimer Disease,” *Europe PMC plus*, May 2018.

[2] A. Kumar, J. Sidhu, A. Goyal, J. W. Tsao, and J. Svercauski, *Alzheimer Disease (Nursing)*. 2021.

[3] M. Nwadiugwu, I. Onwuekwe, E. Ezeanolue, and H. Deng, “Beyond Amyloid: A Machine Learning-Driven Approach Reveals Properties of Potent GSK-3β Inhibitors Targeting Neurofibrillary Tangles,” *Int J Mol Sci*, vol. 25, no. 5, 2024, doi: 10.3390/ijms25052646.

[4] G. G. Glenner and C. W. Wong, “Alzheimer’s disease: Initial report of the purification and characterization of a novel cerebrovascular amyloid protein,” *Biochem Biophys Res Commun*, vol. 120, no. 3, 1984, doi: 10.1016/S0006-291X(84)80190-4.

[5] G. G. Glenner, “Reprint of ‘Alzheimer’s disease: Initial report of the purification and characterization of a novel cerebrovascular amyloid protein,’” *Biochem Biophys Res Commun*, vol. 425, no. 3, 2012, doi: 10.1016/j.bbrc.2012.08.020.

[6] H. Ashrafian, E. H. Zadeh, and R. H. Khan, “Review on Alzheimer’s disease: Inhibition of amyloid beta and tau tangle formation,” 2021. doi: 10.1016/j.ijbiomac.2020.11.192.

[7] Sujan Devkota, Todd D. Williams, and Michael S. Wolfe, “Familial Alzheimer’s disease mutations in amyloid protein precursor alter proteolysis by γ-secretase to increase amyloid β-peptides of ≥45 residues,” 2021.

[8] X. Liu, Y. Liu, and S. Ji, “Secretases related to amyloid precursor protein processing,” 2021. doi: 10.3390/membranes11120983.

[9] R. Vassar, D. M. Kovacs, R. Yan, and P. C. Wong, “The β-secretase enzyme BACE in health and Alzheimer’s disease: Regulation, cell biology, function, and therapeutic potential,” in *Journal of Neuroscience*, 2009. doi: 10.1523/JNEUROSCI.3657-09.2009.

[10] Y. Zhang, H. Chen, R. Li, K. Sterling, and W. Song, “Amyloid β-based therapy for Alzheimer’s disease: challenges, successes and future,” 2023. doi: 10.1038/s41392-023-01484-7.

[11] Y. Cheng, D. Y. Tian, and Y. J. Wang, “Peripheral clearance of brain-derived Aβ in Alzheimer’s disease: Pathophysiology and therapeutic perspectives,” 2020. doi: 10.1186/s40035-020-00195-1.

[12] K. G. Yiannopoulou and S. G. Papageorgiou, “Current and Future Treatments in Alzheimer Disease: An Update,” 2020. doi: 10.1177/1179573520907397.

[13] J. M. Tarasoff-Conway *et al.*, “Clearance systems in the brain - Implications for Alzheimer disease,” 2015. doi: 10.1038/nrneurol.2015.119.

[14] H. Hampel *et al.*, “The Amyloid-β Pathway in Alzheimer’s Disease,” 2021. doi: 10.1038/s41380-021-01249-0.

[15] L. Zuroff, D. Daley, K. L. Black, and M. Koronyo-Hamaoui, “Clearance of cerebral Aβ in Alzheimer’s disease: reassessing the role of microglia and monocytes,” 2017. doi: 10.1007/s00018-017-2463-7.

[16] G. F. Chen *et al.*, “Amyloid beta: Structure, biology and structure-based therapeutic development,” 2017. doi: 10.1038/aps.2017.28.

[17] Sagar Gaikwad *et al.*, “Nasal tau immunotherapy clears intracellular tau pathology and improves cognitive functions in aged tauopathy mice,” *Sci Transl Med*, Feb. 2024.

[18] H. A. Alhazmi and M. Albratty, “An update on the novel and approved drugs for Alzheimer disease,” 2022. doi: 10.1016/j.jsps.2022.10.004.

[19] Q. Huang, C. Liao, F. Ge, J. Ao, and T. Liu, “Acetylcholine bidirectionally regulates learning and memory,” 2022. doi: 10.1016/j.jnrt.2022.100002.

[20] S. M. Bell *et al.*, “Mitochondrial dysfunction in Alzheimer’s disease: A biomarker of the future?,” 2021. doi: 10.3390/biomedicines9010063.

[21] W. Wang, F. Zhao, X. Ma, G. Perry, and X. Zhu, “Mitochondria dysfunction in the pathogenesis of Alzheimer’s disease: Recent advances,” 2020. doi: 10.1186/s13024-020-00376-6.

[22] P. Scheltens *et al.*, “Alzheimer’s disease,” 2021. doi: 10.1016/S0140-6736(20)32205-4.

[23] T. Nedelec *et al.*, “Identifying health conditions associated with Alzheimer’s disease up to 15 years before diagnosis: an agnostic study of French and British health records,” *Lancet Digit Health*, vol. 4, no. 3, 2022, doi: 10.1016/S2589-7500(21)00275-2.

[24] G. Tini *et al.*, “Alzheimer’s Disease and Cardiovascular Disease: A Particular Association,” 2020. doi: 10.1155/2020/2617970.

[25] G. D. Stanciu *et al.*, “Link between diabetes and Alzheimer’s disease due to the shared amyloid aggregation and deposition involving both neurodegenerative changes and neurovascular damages,” 2020. doi: 10.3390/jcm9061713.

[26] Carmine Finelli, “Metabolic syndrome, alzheimer’s disease, and Covid 19: a possible correlation. Current Alzheimer Research.,” *Metabolic syndrome*, 2021.

[27] Marcello Ciaccio *et al.*, “COVID-19 and Alzheimer’s Disease ,” *Brain Sci*, 2021.

[28] C. Villa, E. Rivellini, M. Lavitrano, and R. Combi, “Can SARS-CoV-2 Infection Exacerbate Alzheimer’s Disease? An Overview of Shared Risk Factors and Pathogenetic Mechanisms,” 2022. doi: 10.3390/jpm12010029.

[29] M. H. Haghir Ebrahim Abadi *et al.*, “AI-driven covalent drug design strategies targeting main protease (mpro) against SARS-CoV-2: structural insights and molecular mechanisms,” 2024. doi: 10.1080/07391102.2024.2308769.

[30] S. Zhang, H. Dong, J. Bian, D. Li, and C. Liu, “Targeting amyloid proteins for clinical diagnosis of neurodegenerative diseases,” 2023. doi: 10.1016/j.fmre.2022.10.009.

[31] M. Khorshid, J. Varshosaz, M. Rostami, F. Haghiralsadat, V. Akbari, and P. Khorshid, “Anti HER-2 aptamer functionalized gold nanoparticles of dasatinib for targeted chemo-radiotherapy in breast cancer cells,” *Biomaterials Advances*, vol. 154, 2023, doi: 10.1016/j.bioadv.2023.213591.

[32] L. Jönsson *et al.*, “The affordability of lecanemab, an amyloid-targeting therapy for Alzheimer’s disease: an EADC-EC viewpoint,” 2023. doi: 10.1016/j.lanepe.2023.100657.

[33] W. Wu *et al.*, “The FDA-approved anti-amyloid-β monoclonal antibodies for the treatment of Alzheimer’s disease: a systematic review and meta-analysis of randomized controlled trials,” 2023. doi: 10.1186/s40001-023-01512-w.

[34] M. Shi, F. Chu, F. Zhu, and J. Zhu, “Impact of Anti-amyloid-β Monoclonal Antibodies on the Pathology and Clinical Profile of Alzheimer’s Disease: A Focus on Aducanumab and Lecanemab,” 2022. doi: 10.3389/fnagi.2022.870517.

[35] E. Fedele, “Anti-Amyloid Therapies for Alzheimer’s Disease and the Amyloid Cascade Hypothesis,” 2023. doi: 10.3390/ijms241914499.

[36] J. Cummings, A. M. L. Osse, D. Cammann, J. Powell, and J. Chen, “Anti-Amyloid Monoclonal Antibodies for the Treatment of Alzheimer’s Disease,” *BioDrugs*, vol. 38, no. 1, pp. 5–22, Jan. 2024, doi: 10.1007/s40259-023-00633-2.

[37] R. Brockmann, J. Nixon, B. L. Love, and I. Yunusa, “Impacts of FDA approval and Medicare restriction on antiamyloid therapies for Alzheimer’s disease: patient outcomes, healthcare costs, and drug development,” 2023. doi: 10.1016/j.lana.2023.100467.

[38] G. E. Vitek, B. Decourt, and M. N. Sabbagh, “Lecanemab (BAN2401): an anti–beta-amyloid monoclonal antibody for the treatment of Alzheimer disease,” *Expert Opin Investig Drugs*, vol. 32, no. 2, 2023, doi: 10.1080/13543784.2023.2178414.

[39] S. Chowdhury and N. S. Chowdhury, “Novel anti-amyloid-beta (Aβ) monoclonal antibody lecanemab for Alzheimer’s disease: A systematic review,” *Int J Immunopathol Pharmacol*, vol. 37, 2023, doi: 10.1177/03946320231209839.

[40] K. Sharma, “Cholinesterase inhibitors as Alzheimer’s therapeutics (Review),” 2019. doi: 10.3892/mmr.2019.10374.

[41] G. Marucci, M. Buccioni, D. D. Ben, C. Lambertucci, R. Volpini, and F. Amenta, “Efficacy of acetylcholinesterase inhibitors in Alzheimer’s disease,” 2021. doi: 10.1016/j.neuropharm.2020.108352.

[42] N. Nicosia, M. Giovenzana, P. Misztak, J. Mingardi, and L. Musazzi, “Glutamate-Mediated Excitotoxicity in the Pathogenesis and Treatment of Neurodevelopmental and Adult Mental Disorders,” *Int J Mol Sci*, vol. 25, no. 12, p. 6521, Jun. 2024, doi: 10.3390/ijms25126521.

[43] R. D. Andrew *et al.*, “Questioning Glutamate Excitotoxicity in Acute Brain Damage: The Importance of Spreading Depolarization,” *Neurocrit Care*, vol. 37, 2022, doi: 10.1007/s12028-021-01429-4.

[44] J. Y. Magdaleno Roman and C. Chapa González, “Glutamate and excitotoxicity in central nervous system disorders: ionotropic glutamate receptors as a target for neuroprotection,” *Neuroprotection*, vol. 2, no. 2, pp. 137–150, Jun. 2024, doi: 10.1002/nep3.46.

[45] C. G. Parsons, W. Danysz, A. Dekundy, and I. Pulte, “Memantine and cholinesterase inhibitors: Complementary mechanisms in the treatment of Alzheimer’s disease,” 2013. doi: 10.1007/s12640-013-9398-z.

[46] Y. Karaman, F. Erdoğan, E. Köseoğlu, T. Turan, and A. Ö. Ersoy, “A 12-month study of the efficacy of rivastigmine in patients with advanced moderate alzheimer’s disease,” *Dement Geriatr Cogn Disord*, vol. 19, no. 1, 2005, doi: 10.1159/000080972.

[47] M. R. Farlow, A. Hake, J. Messina, R. Hartman, J. Veach, and R. Anand, “Response of patients with Alzheimer disease to rivastigmine treatment is predicted by the rate of disease progression,” *Arch Neurol*, vol. 58, no. 3, 2001, doi: 10.1001/archneur.58.3.417.

[48] M. Farlow, R. Anand, J. Messina, R. Hartman, and J. Veach, “A 52-week study of the efficacy of rivastigmine in patients with mild to moderately severe Alzheimer’s disease,” *Eur Neurol*, vol. 44, no. 4, 2000, doi: 10.1159/000008243.

[49] M. Farlow, S. Potkin, B. Koumaras, J. Veach, and D. Mirski, “Analysis of outcome in retrieved dropout patients in a Rivastigmine vs Placebo, 26-week, Alzheimer disease trial,” *Arch Neurol*, vol. 60, no. 6, 2003, doi: 10.1001/archneur.60.6.843.

[50] M. Rösler *et al.*, “Efficacy and safety of rivastigmine in patients with Alzheimer’s disease: International randomised controlled trial,” *Br Med J*, vol. 318, no. 7184, 1999.

[51] B. Reisberg, R. Doody, A. Stöffler, F. Schmitt, S. Ferris, and H. J. Möbius, “Memantine in Moderate-to-Severe Alzheimer’s Disease,” *New England Journal of Medicine*, vol. 348, no. 14, 2003, doi: 10.1056/nejmoa013128.

[52] S. Bakchine and H. Loft, “Memantine treatment in patients with mild to moderate Alzheimer’s disease: Results of a randomised, double-blind, placebo-controlled 6-month study (Journal of Alzheimer’s Disease),” 2008. doi: 10.3233/JAD-2008-13110.

[53] U. Richarz, M. Gaudig, K. Rettig, and B. Schauble, “Galantamine treatment in outpatients with mild Alzheimer’s disease,” *Acta Neurol Scand*, vol. 129, no. 6, 2014, doi: 10.1111/ane.12195.

[54] H. Brodaty, J. Corey-Bloom, F. C. V. Potocnik, L. Truyen, M. Gold, and C. R. V. Damaraju, “Galantamine prolonged-release formulation in the treatment of mild to moderate Alzheimer’s disease,” *Dement Geriatr Cogn Disord*, vol. 20, no. 2–3, 2005, doi: 10.1159/000086613.

[55] L. M. Gault *et al.*, “ABT-126 monotherapy in mild-to-moderate Alzheimer’s dementia: Randomized double-blind, placebo and active controlled adaptive trial and open-label extension,” *Alzheimers Res Ther*, vol. 8, no. 1, 2016, doi: 10.1186/s13195-016-0210-1.

[56] H. Fukuda, M. Maeda, F. Murata, and Y. Murata, “Anti-Dementia Drug Persistence Following Donepezil Initiation Among Alzheimer’s Disease Patients in Japan: LIFE Study,” *Journal of Alzheimer’s Disease*, vol. 90, no. 3, 2022, doi: 10.3233/JAD-220200.

[57] A. Burns *et al.*, “The Effects of Donepezil in Alzheimer’s Disease – Results from a Multinational Trial¹,” *Dement Geriatr Cogn Disord*, vol. 10, no. 3, pp. 237–244, 1999, doi: 10.1159/000017126.

[58] R. R. Tampi, B. P. Forester, and M. Agronin, “Aducanumab: Evidence from clinical trial data and controversies,” 2021. doi: 10.7573/dic.2021-7-3.

[59] J. Sevigny *et al.*, “The antibody aducanumab reduces Aβ plaques in Alzheimer’s disease,” *Nature*, vol. 537, no. 7618, 2016, doi: 10.1038/nature19323.

[60] J. Ferrero *et al.*, “First-in-human, double-blind, placebo-controlled, single-dose escalation study of aducanumab (BIIB037) in mild-to-moderate Alzheimer’s disease,” *Alzheimer’s and Dementia: Translational Research and Clinical Interventions*, vol. 2, no. 3, 2016, doi: 10.1016/j.trci.2016.06.002.

[61] Y. Karaman, F. Erdoğan, E. Köseoğlu, T. Turan, and A. Ö. Ersoy, “A 12-Month Study of the Efficacy of Rivastigmine in Patients with Advanced Moderate Alzheimer’s Disease,” *Dement Geriatr Cogn Disord*, vol. 19, no. 1, pp. 51–56, 2005, doi: 10.1159/000080972.

[62] F. R. Weth *et al.*, “Unlocking hidden potential: advancements, approaches, and obstacles in repurposing drugs for cancer therapy,” 2024. doi: 10.1038/s41416-023-02502-9.

[63] Y. Qiu and F. Cheng, “Artificial intelligence for drug discovery and development in Alzheimer’s disease,” *Curr Opin Struct Biol*, vol. 85, p. 102776, Apr. 2024, doi: 10.1016/j.sbi.2024.102776.

[64] J. Cummings, Y. Zhou, G. Lee, K. Zhong, J. Fonseca, and F. Cheng, “Alzheimer’s disease drug development pipeline: 2023,” *Alzheimer’s & Dementia: Translational Research & Clinical Interventions*, vol. 9, no. 2, 2023, doi: 10.1002/trc2.12385.

[65] W. R. Reay and M. J. Cairns, “Advancing the use of genome-wide association studies for drug repurposing,” *Nat Rev Genet*, vol. 22, no. 10, pp. 658–671, Oct. 2021, doi: 10.1038/s41576-021-00387-z.

[66] J. Zhang, Y. Wang, Y. Zhang, and J. Yao, “Genome-wide association study in Alzheimer’s disease: a bibliometric and visualization analysis,” *Front Aging Neurosci*, vol. 15, 2023, doi: 10.3389/fnagi.2023.1290657.

[67] R. Mishra and B. Li, “The application of artificial intelligence in the genetic study of Alzheimer’s disease,” 2020. doi: 10.14336/AD.2020.0312.

[68] S. J. Andrews, A. E. Renton, B. Fulton-Howard, A. Podlesny-Drabiniok, E. Marcora, and A. M. Goate, “The complex genetic architecture of Alzheimer’s disease: novel insights and future directions,” 2023. doi: 10.1016/j.ebiom.2023.104511.

[69] M. Squillario *et al.*, “A telescope GWAS analysis strategy, based on SNPs-genes-pathways ensamble and on multivariate algorithms, to characterize late onset Alzheimer’s disease,” *Sci Rep*, vol. 10, no. 1, 2020, doi: 10.1038/s41598-020-67699-8.

[70] J. C. Lambert, A. Ramirez, B. Grenier-Boley, and C. Bellenguez, “Step by step: towards a better understanding of the genetic architecture of Alzheimer’s disease,” 2023. doi: 10.1038/s41380-023-02076-1.

[71] A. S. Khaire, C. E. Wimberly, E. C. Semmes, J. H. Hurst, and K. M. Walsh, “An integrated genome and phenome-wide association study approach to understanding Alzheimer’s disease predisposition,” *Neurobiol Aging*, vol. 118, 2022, doi: 10.1016/j.neurobiolaging.2022.05.011.

[72] S. J. Andrews, B. Fulton-Howard, and A. Goate, “Interpretation of risk loci from genome-wide association studies of Alzheimer’s disease,” 2020. doi: 10.1016/S1474-4422(19)30435-1.

[73] S. Vatansever *et al.*, “Artificial intelligence and machine learning-aided drug discovery in central nervous system diseases: State-of-the-arts and future directions,” 2021. doi: 10.1002/med.21764.

[74] S. K. Niazi, “The Coming of Age of AI/ML in Drug Discovery, Development, Clinical Testing, and Manufacturing: The FDA Perspectives,” *Drug Des Devel Ther*, vol. 17, 2023, doi: 10.2147/DDDT.S424991.

[75] S. Mirkin and B. C. Albensi, “Should artificial intelligence be used in conjunction with Neuroimaging in the diagnosis of Alzheimer’s disease?,” *Front Aging Neurosci*, vol. 15, Apr. 2023, doi: 10.3389/fnagi.2023.1094233.

[76] M. A. Deture and D. W. Dickson, “The neuropathological diagnosis of Alzheimer’s disease,” 2019. doi: 10.1186/s13024-019-0333-5.

[77] Q. Zhu *et al.*, "Classification of Alzheimer's Disease Based on Abnormal Hippocampal Functional Connectivity and Machine Learning," *Front Aging Neurosci*, vol. 14, 2022, doi: 10.3389/fnagi.2022.754334.

[78] A. Subasi, M. N. Kapadnis, and A. K. Bulbul, "Alzheimer's disease detection using artificial intelligence," in *Augmenting Neurological Disorder Prediction and Rehabilitation Using Artificial Intelligence*, 2022. doi: 10.1016/B978-0-323-90037-9.00011-4.

[79] J. Zhang, B. Zheng, A. Gao, X. Feng, D. Liang, and X. Long, "A 3D densely connected convolution neural network with connection-wise attention mechanism for Alzheimer's disease classification," *Magn Reson Imaging*, vol. 78, 2021, doi: 10.1016/j.mri.2021.02.001.

[80] D. Lu *et al.*, "Multimodal and Multiscale Deep Neural Networks for the Early Diagnosis of Alzheimer's Disease using structural MR and FDG-PET images," *Sci Rep*, vol. 8, no. 1, 2018, doi: 10.1038/s41598-018-22871-z.

[81] W. Yu *et al.*, "Morphological Feature Visualization of Alzheimer's Disease via Multidirectional Perception GAN," *IEEE Trans Neural Netw Learn Syst*, vol. 34, no. 8, 2023, doi: 10.1109/TNNLS.2021.3118369.

[82] S. El-Sappagh, J. M. Alonso, S. M. R. Islam, A. M. Sultan, and K. S. Kwak, "A multilayer multimodal detection and prediction model based on explainable artificial intelligence for Alzheimer's disease," *Sci Rep*, vol. 11, no. 1, 2021, doi: 10.1038/s41598-021-82098-3.

[83] R. Qureshi *et al.*, "AI in drug discovery and its clinical relevance," 2023. doi: 10.1016/j.heliyon.2023.e17575.

[84] D. Paul, G. Sanap, S. Shenoy, D. Kalyane, K. Kalia, and R. K. Tekade, "Artificial intelligence in drug discovery and development," *Drug Discov Today*, vol. 26, no. 1, pp. 80–93, Jan. 2021, doi: 10.1016/j.drudis.2020.10.010.

[85] C. Fabrizio, A. Termine, C. Caltagirone, and G. Sancesario, "Artificial intelligence for Alzheimer's disease: Promise or challenge?," *Diagnostics*, vol. 11, no. 8, 2021, doi: 10.3390/diagnostics11081473.

[86] M. M. Taye, "Understanding of Machine Learning with Deep Learning: Architectures, Workflow, Applications and Future Directions," 2023. doi: 10.3390/computers12050091.

[87] M. M. Taye, "Understanding of Machine Learning with Deep Learning: Architectures, Workflow, Applications and Future Directions," 2023. doi: 10.3390/computers12050091.

[88] Y. Xu *et al.*, "Artificial intelligence: A powerful paradigm for scientific research," 2021. doi: 10.1016/j.xinn.2021.100179.

[89] Z. Ahmed, S. Wan, F. Zhang, and W. Zhong, "Artificial intelligence for omics data analysis," *BMC Methods*, vol. 1, no. 1, p. 4, May 2024, doi: 10.1186/s44330-024-00004-5.

[90] D. Jungwirth and D. Haluza, "Artificial Intelligence and Public Health: An Exploratory Study," *Int J Environ Res Public Health*, vol. 20, no. 5, 2023, doi: 10.3390/ijerph20054541.

[91] F. Cheng *et al.*, "Artificial intelligence and open science in discovery of disease-modifying medicines for Alzheimer's disease," 2024. doi: 10.1016/j.xcrm.2023.101379.

[92] W. Yu and A. D. Mackerell, “Computer-aided drug design methods,” in *Methods in Molecular Biology*, vol. 1520, 2017. doi: 10.1007/978-1-4939-6634-9_5.

[93] Y. Lin, “Review of Modern Computer-aided Drug Design Methods,” *International Journal of Biology and Life Sciences*, vol. 1, no. 1, 2022, doi: 10.54097/ijbls.v1i1.3230.

[94] F. Gentile *et al.*, “Artificial intelligence–enabled virtual screening of ultra-large chemical libraries with deep docking,” 2022. doi: 10.1038/s41596-021-00659-2.

[95] S. K. Niazi and Z. Mariam, “Computer-Aided Drug Design and Drug Discovery: A Prospective Analysis,” 2024. doi: 10.3390/ph17010022.

[96] D. Crucitti, C. Pérez Míguez, J. Á. Díaz Arias, D. B. Fernandez Prada, and A. Mosquera Orgueira, “De novo drug design through artificial intelligence: an introduction,” *Frontiers in Hematology*, vol. 3, 2024, doi: 10.3389/frhem.2024.1305741.

[97] S. Pandey and B. K. Singh, “De-novo Drug Design, Molecular Docking and In-Silico Molecular Prediction of AChEI Analogues through CADD Approaches as Anti-Alzheimer’s Agents,” *Curr Comput Aided Drug Des*, vol. 16, no. 1, 2019, doi: 10.2174/1573409915666190301124210.

[98] V. D. Mouchlis *et al.*, “Advances in de novo drug design: From conventional to machine learning methods,” 2021. doi: 10.3390/ijms22041676.

[99] A. Nunes-Alves and K. Merz, “AlphaFold2 in Molecular Discovery,” 2023. doi: 10.1021/acs.jcim.3c01459.

[100] V. Scardino, J. I. Di Filippo, and C. N. Cavasotto, “How good are AlphaFold models for docking-based virtual screening?,” *iScience*, vol. 26, no. 1, 2023, doi: 10.1016/j.isci.2022.105920.

[101] F. Palazzesi and A. Pozzan, “Deep Learning Applied to Ligand-Based De Novo Drug Design,” in *Methods in Molecular Biology*, vol. 2390, 2022. doi: 10.1007/978-1-0716-1787-8_12.

[102] Y. Fang, X. Pan, and H. Bin Shen, “De novo drug design by iterative multiobjective deep reinforcement learning with graph-based molecular quality assessment,” *Bioinformatics*, vol. 39, no. 4, 2023, doi: 10.1093/bioinformatics/btad157.

[103] K. Gao, D. D. Nguyen, M. Tu, and G. W. Wei, “Generative Network Complex for the Automated Generation of Drug-like Molecules,” *J Chem Inf Model*, vol. 60, no. 12, 2020, doi: 10.1021/acs.jcim.0c00599.

[104] A. C. Good, S. R. Krystek, and J. S. Mason, “High-throughput and virtual screening: Core lead discovery technologies move towards integration,” 2000. doi: 10.1016/S1359-6446(00)80056-2.

[105] K. A. Carpenter and X. Huang, “Machine Learning-based Virtual Screening and Its Applications to Alzheimer’s Drug Discovery: A Review,” *Curr Pharm Des*, vol. 24, no. 28, 2018, doi: 10.2174/1381612824666180607124038.

[106] T. Doherty *et al.*, “Artificial intelligence for dementia drug discovery and trials optimization,” 2023. doi: 10.1002/alz.13428.

[107] L. Di and E. H. Kerns, *Drug-Like Properties: Concepts, Structure Design and Methods from ADME to Toxicity Optimization*. 2016. doi: 10.1016/C2013-0-18378-X.

[108] M. J. Waring *et al.*, “An analysis of the attrition of drug candidates from four major pharmaceutical companies,” 2015. doi: 10.1038/nrd4609.

[109] M. Ahmadi, B. Alizadeh, S. M. Ayyoubzadeh, and M. Abiyarghamsari, “Predicting Pharmacokinetics of Drugs Using Artificial Intelligence Tools: A Systematic Review,” 2024. doi: 10.1007/s13318-024-00883-7.

[110] F. Cheng and J. Cummings, “Artificial Intelligence in Alzheimer’s Drug Discovery,” in *Alzheimer’s Disease Drug Development*, 2022. doi: 10.1017/9781108975759.007.

[111] A. M. Lanzi, A. K. Saylor, D. Fromm, H. Liu, B. Macwhinney, and M. L. Cohen, “DementiaBank: Theoretical Rationale, Protocol, and Illustrative Analyses,” *Am J Speech Lang Pathol*, vol. 32, no. 2, 2023, doi: 10.1044/2022_AJSLP-22-00281.

[112] F. Cheng and J. Cummings, “Artificial Intelligence in Alzheimer’s Drug Discovery,” in *Alzheimer’s Disease Drug Development*, 2022. doi: 10.1017/9781108975759.007.

[113] A. Davis, W. Mendoza, D. Leach, and O. Marques, “Predicting Alzheimer’s Disease with Multi-Omic Data: A Systematic Review,” *medRxiv*, 2022.

[114] A. J. Saykin *et al.*, “Genetic studies of quantitative MCI and AD phenotypes in ADNI: Progress, opportunities, and plans,” 2015. doi: 10.1016/j.jalz.2015.05.009.

[115] C. J. Weber *et al.*, “The Worldwide Alzheimer’s Disease Neuroimaging Initiative: ADNI-3 updates and global perspectives,” *Alzheimer’s and Dementia: Translational Research and Clinical Interventions*, vol. 7, no. 1, 2021, doi: 10.1002/trc2.12226.

[116] A. Kuzma *et al.*, “NIAGADS: The NIA Genetics of Alzheimer’s Disease Data Storage Site,” *Alzheimer’s & Dementia*, vol. 12, no. 11, 2016, doi: 10.1016/j.jalz.2016.08.018.

[117] J. Fang *et al.*, “Artificial intelligence framework identifies candidate targets for drug repurposing in Alzheimer’s disease,” *Alzheimers Res Ther*, vol. 14, no. 1, 2022, doi: 10.1186/s13195-021-00951-z.

[118] Q. Wang *et al.*, “A Bayesian framework that integrates multi-omics data and gene networks predicts risk genes from schizophrenia GWAS data,” *Nat Neurosci*, vol. 22, no. 5, 2019, doi: 10.1038/s41593-019-0382-7.

[119] S. Dara, S. Dhamercherla, S. S. Jadav, C. M. Babu, and M. J. Ahsan, “Machine Learning in Drug Discovery: A Review,” *Artif Intell Rev*, vol. 55, no. 3, 2022, doi: 10.1007/s10462-021-10058-4.

[120] E. Sügis *et al.*, “HENA, heterogeneous network-based data set for Alzheimer’s disease,” *Sci Data*, vol. 6, no. 1, 2019, doi: 10.1038/s41597-019-0152-0.

[121] F. Cheng *et al.*, “Artificial intelligence and open science in discovery of disease-modifying medicines for Alzheimer’s disease,” 2024. doi: 10.1016/j.xcrm.2023.101379.

[122] Exscientia, “Third clinical molecule from collaboration with Sumitomo Pharma to enter Phase 1 trials DSP-2342, a dual 5-HT2A/5-HT7 antagonist to be assessed in psychiatric disease,” *Exscientia*, pp. 5–15, 2023.

[123] E. T. C. Huang *et al.*, “Predicting blood–brain barrier permeability of molecules with a large language model and machine learning,” *Sci Rep*, vol. 14, no. 1, p. 15844, Jul. 2024, doi: 10.1038/s41598-024-66897-y.

[124] C. Yan *et al.*, “Leveraging generative AI to prioritize drug repurposing candidates for Alzheimer’s disease with real-world clinical validation,” *NPJ Digit Med*, vol. 7, no. 1, 2024, doi: 10.1038/s41746-024-01038-3.

[125] D. M. Lyall *et al.*, “Artificial intelligence for dementia—Applied models and digital health,” 2023. doi: 10.1002/alz.13391.

[126] Y. Xu *et al.*, “Exploring patient medication adherence and data mining methods in clinical big data: A contemporary review,” 2023. doi: 10.1111/jebm.12548.

[127] Q. Liu *et al.*, “Personalised treatment for cognitive impairment in dementia: development and validation of an artificial intelligence model,” *BMC Med*, vol. 20, no. 1, 2022, doi: 10.1186/s12916-022-02250-2.

[128] S. H. Chalasani, J. Syed, M. Ramesh, V. Patil, and T. M. Pramod Kumar, “Artificial intelligence in the field of pharmacy practice: A literature review,” 2023. doi: 10.1016/j.rcsop.2023.100346.

[129] E. Barbierato and A. Gatti, “The Challenges of Machine Learning: A Critical Review,” 2024. doi: 10.3390/electronics13020416.

[130] N. M. Safdar, J. D. Banja, and C. C. Meltzer, “Ethical considerations in artificial intelligence,” 2020. doi: 10.1016/j.ejrad.2019.108768.

[131] T. Doherty *et al.*, “Artificial intelligence for dementia drug discovery and trials optimization,” *Alzheimer’s & Dementia*, vol. 19, no. 12, pp. 5922–5933, Dec. 2023, doi: 10.1002/alz.13428.

[132] C. M. Lim, A. González Díaz, M. Fuxreiter, F. W. Pun, A. Zhavoronkov, and M. Vendruscolo, “Multiomic prediction of therapeutic targets for human diseases associated with protein phase separation,” *Proceedings of the National Academy of Sciences*, vol. 120, no. 40, Oct. 2023, doi: 10.1073/pnas.2300215120.