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REVIEW

Artificial intelligence in drug development for delirium and Alzheimer's disease

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Target identification

Abstract Delirium is a common cause and complication of hospitalization in the elderly and is associated with higher risk of future dementia and progression of existing dementia, of which 70% is Alzheimer's disease (AD). AD and delirium, which are known to be aggravated by one another, represent significant societal challenges, especially in light of the absence of effective treatments. The intricate biological mechanisms have led to numerous clinical trial setbacks and likely contribute to the limited efficacy of existing therapeutics. Artificial intelligence (AI) presents a promising avenue for overcoming these hurdles by deploying algorithms to uncover hidden patterns across diverse data types. This review explores the pivotal role of AI in revolutionizing drug discovery for AD and delirium from target identification to the development of small molecule and protein-based therapies. Recent advances in deep learning, particularly in accurate protein structure prediction, are facilitating novel approaches to drug design and expediting the discovery pipeline for biological and small molecule therapeutics. This review concludes with an appraisal of current achievements and limitations, and touches on prospects for the use of AI in advancing drug discovery in AD and delirium, emphasizing its transformative potential in addressing these two and possibly other neurodegenerative conditions.

1. Introduction

Delirium and dementia are two common, currently incurable, brain diseases which likely aggravate one another[1]. Delirium is an acute condition characterized by a disturbance in attention and awareness, with primary features that include an unpredictable course and perceptual abnormalities[2,3]. Risk factors include a range of stressors, such as alcohol use, infection, depression, malnutrition, medications and environment changes, as well as conditions such as hip fracture and severe COVID-19[4-6]. These stressors are often experienced by older individuals with frailty, chronic comorbidities, and other underlying heath conditions[6]. Diagnosis requires at least one additional cognitive impairment, such as deficits in memory, orientation, language, visuospatial ability, or perception to distinguish it from other forms of acute confusion[7,8]. Patients with delirium usually experience fluctuations in mental status throughout the day, which is a cardinal feature rather than evidence for ruling out other conditions[7]. To diagnose delirium, the disturbances cannot be explained by other neurocognitive disorders alone, and there must be clear evidence that the disturbances are caused by a medical condition, trauma, surgery, drug intoxication or withdrawal[9]. Commonly triggered by hospitalization or illness, delirium is associated with poor short- and long-term outcomes, for example, functional and cognitive decline, prolonged hospital stay, more severe hospital-associated complications, increased readmission rates, and increased mortality[2,6,10]. Although delirium occurs in 29%−65% of hospitalized people[2,11], the diagnosis is frequently missed. The consequences of underdiagnosis extend beyond individual health outcomes to impose a substantial economic burden. In the US, the national burden of delirium was estimated to be $143 billion to $152 billion[12]. In a 2019 meta-analysis, the health-care costs for delirium were estimated to range between $806 and $24,509 USD per hospitalised patient[13].

Dementia is a gradual, long-term decline in cognitive abilities, affecting memory, language, orientation, and the capacity to carry out everyday activities[14-16]. Alzheimer's disease (AD) is the most prevalent type of dementia, responsible for up to 70% of cases[17,18]. Typical AD is characterized by significant episodic memory impairment, along with gradual cognitive and functional decline, including diminished word-finding ability, spatial cognition, and executive functions[19,20]. Two key pathological hallmarks of AD are amyloid beta (Aβ) plaques and p-Tau formulated neurofibrillary tangles in the brain, which disrupt normal neuronal functions[21]; other pathological features and contributing factors include inflammation, cell senescence, compromised mitophagy/autophagy, and accumulation of damaged mitochondria, among others[22-25]. It is estimated that 50 million people currently have dementia, and this number is projected to triple by 2050[26]. Associated costs are expected to rise from US $ 1 trillion in 2018 to estimated US $ 2 trillion by 2023[26].

Delirium and dementia have a complicated inter-relationship, with individuals experiencing delirium being at a greater risk of developing dementia[8,27-30]. Moreover, delirium is associated with accelerated long-term cognitive decline[31-34], with AD serving as a classic example of this progression[32]. Dementia and cognitive impairment are also risk factors for developing delirium[27]. Compared to individuals with dementia who do not develop delirium, individuals with both dementia and delirium often face extended hospital stays, more severe cognitive and functional decline, and a higher risk of institutionalization and mortality[35]. AD pathology might affect delirium risk through neuroinflammation and gene−protein interactions[8,36].

Drug development is typically a lengthy, costly, complex, and uncertain process[37,38]. In 2022, bringing a new drug to market was estimated to cost US $1784 million and use more than 13.5 years to develop[39,40]. Even after this lengthy, expensive process, only

5% of drugs are finally approved by the US Food and Drug Administration[40]. New candidate drugs for use in AD treatment, such as nicotinamide adenine dinucleotide oxidized form precursor, urolithin A, and two molecules kaempferol and rhapontigenin identified by artificial intelligence (AI) have been reported[24,41,42]; the clinical efficacy of these molecules is either under testing or still needs to be tested[42]. The development of drugs for use in the central nervous system presents unique challenges including incomplete understanding of underlying mechanisms, limited predictive validity of current animal models (biological perspective), difficulty in designing drugs that can cross the blood−brain barrier (BBB) (chemical perspective), and patient heterogeneity, along with a lack of biomarkers for delirium to confirm engagement of potential targets (clinical perspective)[43,44]. While AD has some well-defined biomarkers (CSF, amyloid PET, tau-PET), the tissues they are located in are not easily accessible[45]; however, this may change with the discovery of blood-based biomarkers. The FDA recently approved lecanemab for AD, an IgG1 monoclonal antibody. While lecanemab has a modest effect on cognitive decline (coupled with substantial risk of serious side-effects), most clinical studies on other drugs have shown poor efficacy or serious adverse reactions in the majority of clinical AD and delirium candidates[46]. For delirium, evidence-based guidelines do not currently recommend the routine use of any drug to treat the condition[47,48]. However, expert opinion supports a role for medication in some situations, for example, where there is intractable patient distress or if the patient's or others' safety is compromised[49]. Given the relationship between delirium and AD, it may also be possible to explore the prevention of AD through the management of delirium[1,8].

Recent advancements in AI, including machine learning (ML) and deep learning (DL) techniques, have shown potential for accelerating drug discovery and improving success rates[50-52]. The strength of AI modeling lies in its ability to learn from extensive historical datasets, extract critical features from multi-omics data, and simultaneously consider multiple parameters for drug design[53-57]. These approaches aim to deepen our understanding of the biological mechanisms underlying AD and delirium, enable the development of drugs with enhanced affinity and PK (pharmacokinetic) profiles, ultimately improving clinical outcomes for these conditions[53,58].

In addition, AI is a rapidly developing field and the, recent success of protein structure prediction models, such as AlphaFold[59], has paved the way for more rational drug design not only for small molecules but also for protein-based therapeutics[59,60]. In this review, we will focus on recent advancements in applying AI to the design of small molecules and protein therapeutics for delirium and AD, specifically reviewing AI technologies used for target identification, drug design, and optimization.

2. Advances in AI modeling for drug discovery: Data representation, modeling techniques, and applications

Recently, AI has advanced rapidly, from the development of large language models like GPT-4 to groundbreaking developments like AlphaFold in protein structure prediction[57,61]. The core focus is on algorithms that leverage high-performance computing resources to analyze large amounts of complex data[62]. Although this review covers a wide range of AI models, they all follow a similar structure that includes data input representation, a main modeling architecture, and the application of different prediction performances for various purposes (Fig. 1).

Data input representation is the process of transforming raw data such as molecular structures, proteins sequences, or biological annotations, which cannot be directly understood by machines, into the matrices and vectors that form machine-learnable data using various computational methods[55,63]. Features and descriptors are used to compute specific properties of the data, creating meaningful numeric representations[63]. For small molecules, descriptors, fingerprints, and SMILES (Simplified Molecular Input Line Entry System, a line notation that encodes molecular structures as computer-friendly text strings) have been developed to encode molecular structures into vectors, capturing the presence and arrangements of atomic substructures, as well as features such as the number of hydrogen donors, acceptors, and molecular weights[64]. In addition to 1D textual representation, 2D graph-based representations have been developed to capture information about neighboring atoms using graph structures[63]. This includes vectors generated by neural networks such as Message Passing Neural Networks (MPNN)[65] and Graph Convolutional Networks (GCNs)[66]. These methods utilize trainable parameters to effectively model the properties of small molecules[65,66]. Furthermore, 3D AI-based molecular representation methods, including voxel-based, point cloud, and graph-based 3D approaches, capture spatial and structural information by leveraging techniques like 3D convolutional networks, geometric DL, and rotationally invariant models[67-69].

Building upon the foundational concepts of 1D, 2D, and 3D representations, more advanced techniques have emerged to better capture specialized biological data types, such as AlphaFold 3 and ESM3 (Evolutionary Scale Modeling) in protein representation[59,70]. AlphaFold 3 leverages Multiple Sequence Alignment to represent evolutionary information, Pair Representation to capture pairwise distances and relationships between amino acid residues, and 3D coordinates for protein sequence embedding[59]. ESM3 represents proteins using large-scale language models trained on protein sequences to learn their underlying biological information. It treats amino acid sequences as a form of 'language' and uses transformer-based architectures to capture relationships between amino acids, learning patterns related to protein structure and function[70]. Different data types require different forms of representation; effective data representation is able to capture essential features, enabling AI models to perform more accurately and efficiently.

Various modeling techniques can be applied to different applications based on the data representation. As shown in Fig. 1, modeling approaches such as Graph Neural Networks (GNNs; including GCNs and MPNN), Recurrent Neural Networks (RNNs), Convolutional Neural Networks, Transformers, and traditional ML models can be applied to general-purpose molecular and protein modeling for tasks such as classification and regression[71]. Additionally, generative models like Variational Autoencoders (VAEs)[72] and Generative Adversarial Networks (GAN)[73]are used for designing new molecular structures and optimizing their properties. Some approaches, such as transformers, involve complex calculations with large parameters, making them more suitable for large datasets[74]. In contrast, methods like Random Forest (RF) are less computationally intensive and can perform well on smaller datasets with simpler representations[75]. There is no single best model; rather, the most suitable model depends on the specific data type and the application. In this review, we do not aim to compare different

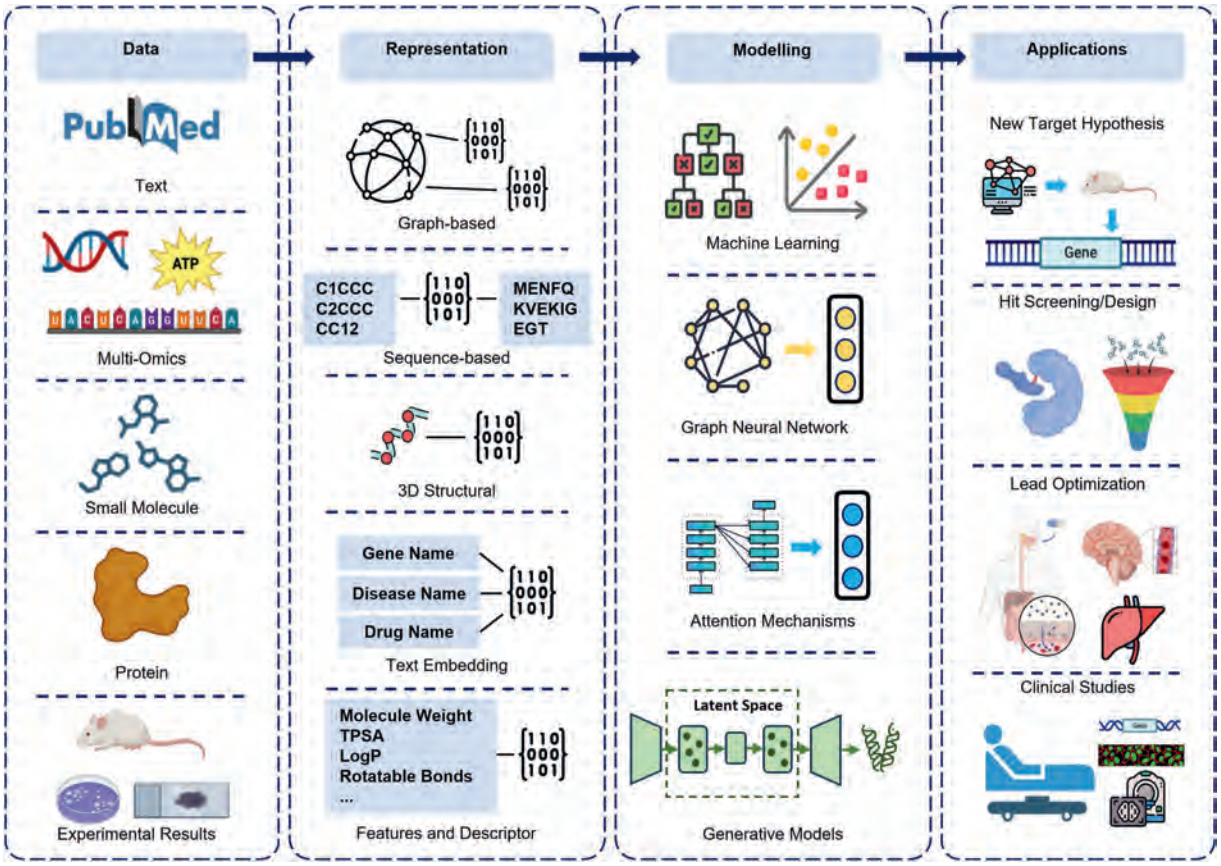

Figure 1 A general workflow on the application of artificial intelligence (AI) Modeling in drug discoveries for delirium and Alzheimer's disease. Based on data availability and the modelling objectives, various sources, including omics data, structures of small molecules and proteins, and experimental and clinical results, can be used as inputs for AI models. These raw data are transformed into matrices and vectors using different data representation techniques to capture essential features. AI models, such as machine learning, graph neural networks, attention mechanisms, and generative models, are then used to reveal hidden patterns from these representations. Depending on the specific applications, different functions and training methods are applied to accomplish tasks such as target hypothesis generation, hit screening, molecule design, lead optimization, or assisting in clinical studies. Figure was generated using BioRender and Flaticon software.

modeling approaches. Instead, we will focus on reviewing their applications in AD and delirium drug discovery.

3. Data resources for delirium and AD discovery

The research community benefits from several disease specialized databases that include multi-omics data for AD and delirium. These databases often encompass genomics, epigenomics, transcriptomics, proteomics, metabolomics, and imaging data, providing comprehensive insights into disease mechanisms, pathological progression, and potential therapeutic targets (Table 1). There are also compounds, proteins, affinity database like protein structural databases (*e.g.*, Protein Data Bank[76], Repository of 3D structures of biological molecules[77]), structure comparison tools[78], protein−protein interaction databases (*e.g.*, Pan Immune Repertoire Database: Validated protein interactions with interface regions[79]), genetic databases (*e.g.*, scRNA-seq datasets[80,81]), and the human reference genome browser[82]. These resources are invaluable in understanding the molecular mechanisms underlying drug interactions and support the development of therapeutic strategies for AD and delirium[83-85]. Furthermore, they facilitate discovery of biomarkers for predicting disease onset, tracking disease progression and assessing drug efficacy in clinical trials[86,87].

4. AI applications in drug discovery

Due to the current state of research and diagnostic challenges, there is a significantly larger focus on AD compared to delirium within the field of AI-driven drug discovery, resulting in many AI applications focusing exclusively on case studies related to AD. However, given the connections between AD and delirium, as well as the broad applicability of AI methodologies, research advances in AI for AD can readily be adapted to delirium studies[8]. This cross-applicability provides a valuable foundation for extending AI-driven insights and techniques from AD research to delirium, ultimately benefiting both fields.

4.1. Target identification for AD and delirium

The standard approach to drug discovery aims to design drug molecules−such as small molecules, peptides, antibodies, or newer modalities like short RNAs or cell therapies−that reverse disease progression by modulating the activity and/or degradation of disease-associated biological targets[52]. The process of selecting a suitable target based on available evidence is known as target identification and prioritization[96,97]. This crucial step aims to ensure that the modulation of the target provides a therapeutic

Table 1 A summary of selected databases for delirium and AD.

Database	Description	Ref.
ADNI	A major resource for imaging and biomarker data for AD research.	88
NIAGADS	Providing genetic data for Alzheimer's research.	89
AD knowledge portal	A platform providing access to data, analyses, and tools for AD research.	90
AIZGPS	A resource for genomics and related research data on AD.	91
TACA	Focusing on clinical and translational research data for AD.	92
HUNT	HUNT databank of the Trøndelag Health Study, a Norwegian population-based health study that collects extensive health and genetic data for research on delirium and AD prevention and public health.	93
UK biobank	The UK biobank is a large-scale biomedical database in the United Kingdom that provides genetic, lifestyle, and health information from 500,000 participants including delirium and AD patients to support medical research.	94
RosMap	The ROS/MAP cohort is a longitudinal study of aging and AD that provides deeply phenotyped clinical, cognitive, neuropathological, and multi-omics data, enabling investigation into the biological mechanisms underlying cognitive decline and dementia.	95

AD: Alzheimer's disease; ADNI: AD Neuroimaging Initiative; AIZGPS: the Alzheimer's Integrated Genetics Program; NIAGADS: National Institute on Aging Genetics of AD Data Storage Site; RosMap: the Religious Orders Study and Memory and Aging Project; TACA: the Translational and Clinical Research AD database.

benefit while maintaining an acceptable safety margin[96,97]. Following target identification, the selected target's role in the disease is validated through *in vivo* studies using disease models, and eventually through clinical trials[96,97]. The identification of drug targets significantly influences the overall success of drug development, guiding the progression from preclinical studies to market[96].

In the context of AD, classical targets include Aβ, tau protein, and cholinergic neurotransmission pathways. The β-amyloid hypothesis has been central to AD drug discovery, with numerous therapies aimed at reducing the generation of amyloid plaques and removal of existing plaques, while tau-targeting approaches seek to prevent tau aggregation and neurofibrillary tangle formation[98]. Additionally, drugs targeting the glutamatergic system and cholinergic deficits, such as acetylcholinesterase (AChE) inhibitors, have been widely used in symptomatic treatment of AD[98]. However, despite decades of research, many therapies targeting these classical pathways have shown limited clinical success, highlighting the need for new strategies (Table 2)[46]. Emerging AI-assisted approaches have uncovered novel targets, such as EPHX2, PLCG2, ABCA7, SORL1, BACE1, and INPP5D, offering deeper insight into AD pathology beyond merely identifying new therapeutic candidates[99].

Modern biology is becoming increasingly data-intensive, encompassing human genetic information from large populations, transcriptomic, proteomic and metabolomics analyses of both healthy and diseased individuals, as well as high-content imaging of clinical material[51,100]. This presents new opportunities to identify novel drug targets, moving beyond classical hypotheses and toward a systems biology approach that incorporates multiple disease mechanisms. However, more effective techniques to handle large-scale multidimensional biological data are required. AI models, including ML and DL, can process and analyze large-scale biological datasets such as genomics, proteomics, and transcriptomics[55,57,97,101]. Unlike traditional methods that rely heavily on predefined hypotheses, AI can uncover novel patterns in high-dimensional data, revealing previously unknown molecular drivers of AD pathology, such as PLCG1[99,102]. These technologies have proven highly effective at identifying molecular targets that traditional methods may overlook, offering a mechanistic understanding of disease pathways and new avenues for therapeutic intervention (Fig. 2).

AD is a progressive condition that requires dynamic analysis of time-series multi-omics data, adding additional challenges to understanding the mechanisms underlying these diseases. Delirium can worsen the progression of AD[103]. DL techniques, particularly RNNs and Long Short-Term Memory models, have proven instrumental in understanding disease progression in neurodegenerative disease due to their ability to process sequential information[104]. These models are particularly adept at analyzing time-series data from multi-omics sources, such as genomics, transcriptomics, and epigenetics, to identify key genetic mutations linked to the onset and progression of AD[104]. AI-driven models have revealed previously underexplored targets like SORL1 and EPHX2[99], which play a role in lipid metabolism and endosomal trafficking in AD.

AI has also facilitated advancements in the prediction of disease driver genes. ML algorithms such as Support Vector Machines and RF have been applied to predict disease-associated genes by analyzing genetic and multi-omics data, aiding in the prioritization of potential therapeutic targets[99,105]. By integrating genetic risk factors with molecular pathway analysis, AI not only identifies candidate genes but also reconstructs disease-associated networks, providing deeper insights into disease progression and possible therapeutic leverage points[102]. For instance, INPP5D[99], a gene associated with immune regulation, was identified through AI-assisted multi-omics analysis as a potential key player in AD (Fig. 2). This approach has proven effective in AD research, where novel genes and pathways implicated in disease progression have been identified[99,105].

Furthermore, AI has demonstrated significant potential in analyzing complex data such as multi-omics. The integration of multi-omics data—combining genomic, transcriptomic, proteomic, and metabolomic datasets—has become a critical component of AI-driven target identification[101,106-108]. By reconstructing disease networks and functional relationships between genes, AI provides a mechanistic understanding of AD that extends beyond target discovery to elucidate disease etiology. This holistic approach offers a comprehensive view of AD pathology, enabling researchers to identify and prioritize new drug targets. AI models have also been used to uncover previously overlooked genetic contributions to AD[106-108]. For example, the AI tool DeepSEA[108] predicted the functional effects of non-coding variants in the *INPP5D* gene, revealing novel variants associated with an

Table 2 A summary on the status of drug candidates against AD (a selected non-exhaustive list).

Drug name	Company	Target pathway	Mechanism	Approval status	Efficacy in patients
Tacrine	Pfizer	Cholinergic system	Acetylcholinesterase inhibitor	Approved (withdrawn)	Moderate symptomatic relief; withdrawn due to safety concerns
Donepezil	Eisai, Pfizer	Cholinergic system	Acetylcholinesterase inhibitor	Approved	Moderate symptomatic relief
Rivastigmine	Novartis	Cholinergic system	Acetylcholinesterase and butyrylcholinesterase inhibitor	Approved	Moderate symptomatic relief
Galantamine	Janssen	Cholinergic system	Acetylcholinesterase inhibitor and nicotinic receptor modulator	Approved	Moderate symptomatic relief
Memantine	Merz pharmaceuticals	Glutamatergic system	NMDA receptor antagonist	Approved	Moderate symptomatic relief
Aducanumab	Biogen, Eisai	Amyloid beta	Monoclonal antibody targeting amyloid protofibrils	Approved (2021) Discontinued (2024)	Controversial, limited efficacy
Lecanemab	Biogen, Eisai	Amyloid beta	Monoclonal antibody targeting amyloid protofibrils	Approved	Slows disease progression
Donanemab	Eli Lilly	Amyloid beta	Monoclonal antibody targeting amyloid protofibrils	Approved (2024)	Slows disease progression
Verubecestat	Merck	APP	BACE1 inhibitor	Discontinued (phase III trials)	No significant clinical benefit, potential for worsening cognition.
Semagacestat	Eli Lilly	APP	Secretase inhibitor	Discontinued (phase III trials)	Worsening of cognitive function, increased risk of skin cancer (basal cell carcinoma). No clinical benefit.
Zagotenemab	Eli Lilly	Tau	Monoclonal antibody targeting tau	Discontinued (2021)	Failed to show efficacy
Tilavonemab	AbbVie	Tau	Monoclonal antibody targeting tau	Discontinued (2019)	Failed to show efficacy
Semorinemab	Genentech, AC immune	Tau	Monoclonal antibody targeting tau	Failed phase II (2021)	Limited efficacy in secondary analyses
Sargramostim	Partner therapeutics	Neuroinflammation	Granulocyte-macrophage colony-stimulating factor (GM-CSF)	Phase II (2021)	Under investigation
Minocycline	Various academic institutions	Neuroinflammation	Anti-inflammatory antibiotic	Inconclusive	Inconclusive results
Pioglitazone	Takeda	Neuroinflammation	Anti-inflammatory effects	Failed phase III	Failed to show efficacy
Intranasal insulin	Various institutions	Metabolic	Modulates brain glucose metabolism	Mixed results	Mixed results
Metformin	Generic	Metabolic	AMPK activator with neuroprotective effects	Under investigation	Under investigation
Blarcamesine (anavex2-73)	Anavex life sciences	Metabolic	Sigma-1 receptor agonist modulating synaptic function	Phase II/III	Potential neuroprotection, under trial
Tideglusib	Zeltia, AMBAR	Metabolic	GSK-3 inhibitor for neuroprotection	Failed phase II	Failed to show efficacy
Idalopirdine	Axovant sciences	5-HT6 receptor	5-HT6 receptor antagonist	Discontinued (phase III trials)	No significant clinical benefit
VG-3927	Vigil neuroscience	TREM2 signaling	TREM2 agonist (small molecule)	Phase II trials	Early data shows promise, including a reduction in TREM2 levels. Further trials are ongoing to determine clinical efficacy

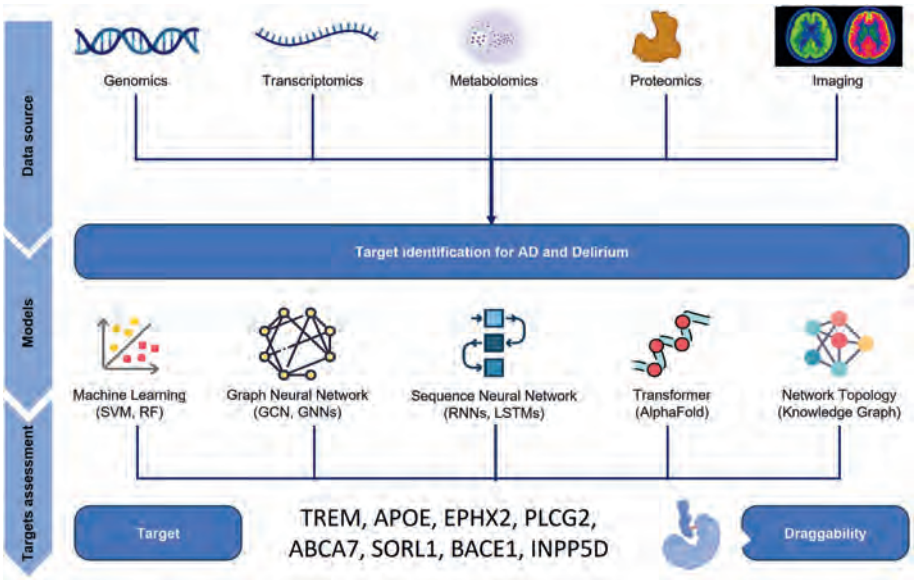

Figure 2 A schematic flow showing how artificial intelligence (AI) can be used for drug target discovery in Alzheimer's disease (AD) and delirium covering data acquisition to drug target identification and assessment. AI models are employed to process large-scale biological datasets such as genomics, transcriptomics, metabolomics, proteomics, and imaging data. Machine learning models (such as Support Vector Machines/SVM, Random Forest/RF), deep learning models (like graph convolutional networks/GCN, Graph Neural Networks/GNNs, RNNs/Recurrent Neural Networks, and Long Short-Term Memory/LSTMs), AlphaFold, and Knowledge Graph can be used jointly in understanding disease progression, prioritizing druggable targets, and predicting disease-driving genes. Figure was generated using BioRender and Flaticon software. The brain image was generated using ChatGPT-4o.

increased risk of late-onset AD[108]. In addition, network-based methods have proven to be highly effective in generating new hypotheses for potential targets in neurodegenerative diseases by leveraging multi-omics data[107,108]. For example, a network DL approach was used to analyze RNA sequencing data, protein−protein interaction (PPI) networks, and gene networks to identify specific microglial subtypes involved in human AD brains[106]. A knowledge graph generated through text mining of literature that integrates gene, disease, and compound information can also be used to generate hypotheses for druggable targets in AD[107].

In addition to genetic data, AI has demonstrated success in generating hypotheses for other omics data, such as disease-associated microRNAs, which regulate gene expression and are involved in AD pathogenesis[109-111]. Neural network models, such as NNMDA, have identified novel miRNA-disease associations, contributing to the discovery of new therapeutic targets for disease[111]. AI-based tools have also been applied to predict alternative splicing events, which play a critical role in gene expression regulation and protein diversity. Tools like AVISPA and DeepChem[112] have enabled more accurate predictions of alternative splicing, aiding in the discovery of new therapeutic opportunities in AD[109,110].

Moreover, protein structure prediction models like AlphaFold 3[59], developed by DeepMind, have demonstrated the potential to accelerate biological research by offering a fast and effective option for modeling protein structures[59]. Compared with experiments such as protein crystallography or cryo-EM tomography, which require months to years to determine structures[113], this package can predict structures within minutes[59]. Beyond drug target identification, AI-powered structural biology allows researchers to explore PPI and novel binding sites, further refining our understanding of AD pathogenesis. This has led to better characterization of targetable structures in protein such as ABCA7[99], which has been implicated in lipid transport and insoluble amyloid level in AD[114]. In addition, the recent development of AlphaFold 3[59] provides new approaches to modeling more complex interactions between proteins and small molecules, nucleic acids, and other proteins[59]. This presents new opportunities for modeling more complex biological mechanisms using predictive models.

Additionally, AI has transformed the druggability assessment of AD-related targets[115,116]. AI models, such as the RF-based SCREEN tool, assess the druggability of proteins by evaluating the geometric and structural features of binding sites. These advancements help prioritize targets with the highest therapeutic potential[116]. AI-based optimization frameworks, particularly those based on reinforcement learning (RL), have also facilitated multi-objective optimization, balancing critical parameters like target potency, selectivity, and permeability[115].

In summary, AI extends beyond the simple identification of new therapeutic targets by enabling a more profound understanding of AD pathology through the integration of multi-omics, disease progression modeling, and neural network and biological network-based analyses. Unlike conventional methods that focus primarily on known pathways such Aβ and tau, AI-driven approaches uncover novel targets, including EPHX2, PLCG2, ABCA7, SORL1, and INPP5D[99] (Fig. 2). These discoveries refine disease mechanisms and enhance druggability assessment. This shift from a single-target paradigm to a systems biology approach represents a transformative advancement in AD research, accelerating the development of effective treatments[117].

4.2. *Small molecule drug design and optimization*

Small molecule drugs, defined as low molecular weight organic compounds, have dominated the pharmaceutical industry for nearly a century due to advantages such as oral administration, the ability to cross cell membranes to reach intracellular targets, and flexible design options to engage biological targets through various modes of action[118]. Five small-molecule drugs, including tacrine, donepezil, rivastigmine, galantamine, and memantine, which inhibit AChE or act as antagonists to *N*-methyl-D-aspartate receptors to alleviate AD and delirium symptoms, were approved in the 1990s and 2000s[46].

Small molecule drug discovery involves identifying or designing molecules with high selectivity and potency to effectively modulate target proteins by inhibiting, activating or degrading them[118]. Suitable candidate compounds must undergo further optimization to improve pharmacodynamic and pharmacokinetic (PK) properties, mitigate toxicity, and maintain efficacy[118]. Studies have demonstrated that AI can potentially significantly speed up this process for AD and delirium[52] drug discovery. This section will review various applications, including virtual screening (VS), *de novo* drug design, drug repurposing, compound−target interaction prediction, and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) optimizations (Fig. 3, Table 3).

4.2.1. *VS*

The initial step in small molecule drug design is to find compounds with a high potential to bind to a drug target, known as "hits". Good hits are important for drug discovery as they serve as the starting points for developing potent and selective drug candidates[136]. There are multiple successful case studies demonstrating the effective application of virtual screening (VS) in selecting promising compounds across various diseases[137-141].

VS is an effective and widely adopted computational approach for hit discovery. It follows a step by step filtering procedure, including different criteria such as molecule size, ligand similarity, and predicted physicochemical and PK properties in order to select suitable compounds from a large compound library[142]. There are two main approaches: ligand-based VS (LBVS), which relies on known active compounds to find similar molecules, and structure-based VS structure-based VS (SBVS), which uses the 3D structure of the target protein. VS helps prioritize compounds for experimental validation and has been shown to be effective across multiple studies for discovering hits for AD[119,120,143-146].

For LBVS, researchers focus on generating molecular representation matrices that encode the structural and functional characteristics of molecules based on DL or rule-based approaches[55,119,120,143,145,146]. For instance, a workflow was developed using vector representations of molecular structures,

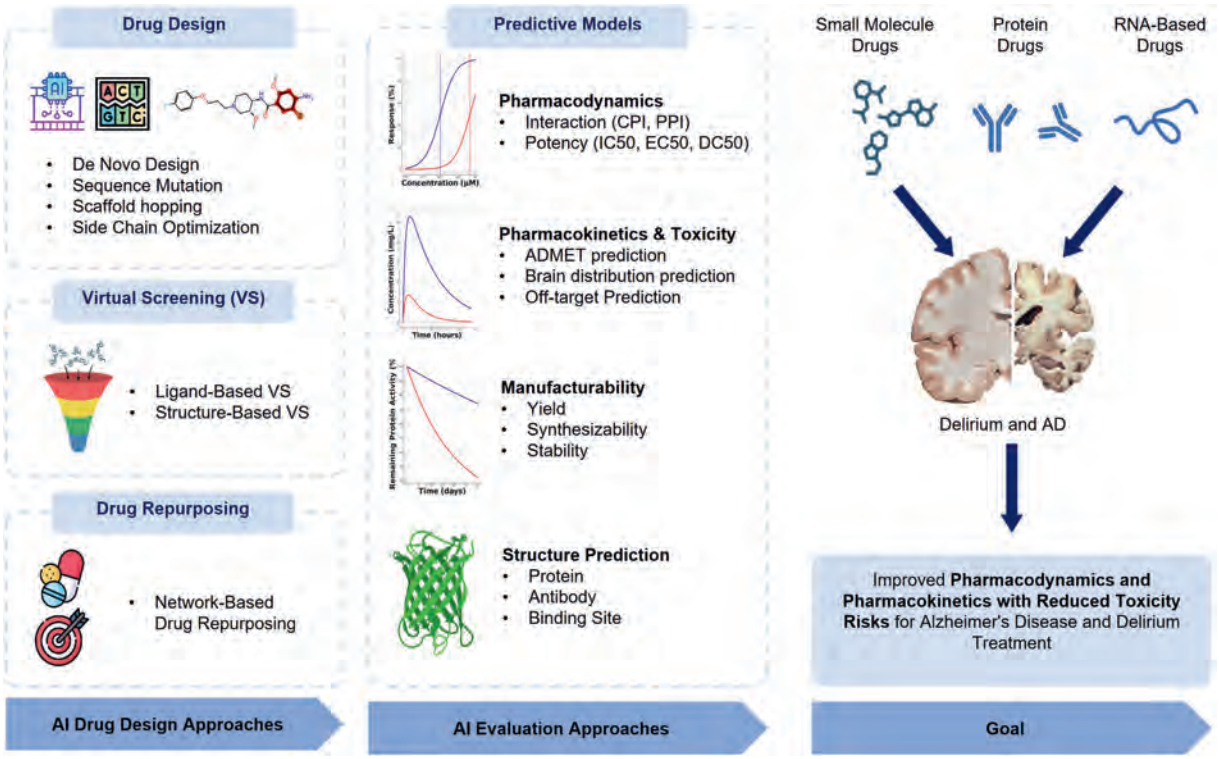

Figure 3 A summary of the broad applications of AI in the development of small molecule- and protein (*e.g.*, antibody)-based drug candidates for delirium and AD. Many current AI models in drug design aim to enhance pharmacodynamics and pharmacokinetics while reducing toxicity risks. AI-driven approaches such as drug design, virtual screening, and drug repurposing, along with predictive models for molecular properties, are employed to achieve this goal. These methods enable the automatic selection of drug candidates with desirable characteristics based on predicted results, aiding the development of small molecule and protein-based therapeutics for these conditions. ADMET: Absorption Distribution Metabolism Excretion and Toxicity; CPI: compound−protein interaction; DC_{50}: half-maximal drug concentration; EC_{50}: half-maximal effective concentration; IC_{50}: half-maximal inhibitory concentration; PPI: protein−protein interaction; VS: virtual screening. Figure was generated using BioRender and Flaticon software.

Table 3 A summary of different AI models in the designing and optimizing of small molecule drug candidates for delirium and AD.

Model	Target	Approach description	Result	Ref.
VS				
Pretrained representation model for LBVS	Mitophagy inducers	LBVS workflow that utilized a pretraining process to learn a molecular representation model from a library of 19.9 million compounds	Two inducers validated in animal models	42
Multiple ML	β-Amyloid	A molecular property filter based on charge, molecular weight, and log*P*, alongside ML models using simple chemical descriptors and 3D field points in forge software for shape and surface properties.	Five compounds validated in molecular-level experiments	119
ML	Dual 5-HT6/5-HT2A receptor	The process included 2D fingerprint screening, ADMET filtering, 3D pharmacophore screening, and flexible docking, resulting in the selection of 92 compounds for *in vitro* binding affinity evaluation.	Fourteen compounds validated in molecular-level experiments	120
VirtualFlow	KEAP1	A highly automated and versatile open-source platform with perfect scaling behavior for screening ultra-large libraries	One compound validated in molecular-level experiments	121
De novo drug design				
Wasserstein GAN	BACE1	The framework utilizes a Wasserstein GAN with gradient penalty, which can generate new molecular structures using the generator and evaluate their bioactivity and BBB permeability using the discriminator.	Generation of over 1,000,000 new molecules with favorable properties.	122
RationaleRL	JNK3; GSK3β	The generative model constructs molecules as combinations of multiple rationale completions, fine-tuning the mixture to maintain the desired properties.	Generate new molecules with favorable properties.	123
Drug repurposing				
NETTAG	Multipletargets	A topology-based DL framework integrates multi-omics data with the human PPI network to predict drug repurposing candidates.	Four drugs supported by literature evidence	124
Network-based, multimodal approach	Multipletargets	A network-based, multimodal approach for drug discovery informed by single-cell/nucleus genomics.	Fluticasone and mometasone have been identified as potential treatments for AD	125
DRIAD	Multipletargets	A machine learning framework that quantifies potential associations between Alzheimer's disease severity, measured by braak stage, and molecular mechanisms represented in gene lists.	Network that supports AD-related drug discovery	126
AI-DrugNet	Multipletargets	Integrated drug and target features, with drug−target pairs as nodes and their associations as edges in the AD network, including drug−drug, target−target, and drug−target relationships.	Network that supports AD-related drug discovery	127
Compound target interactions prediction				
QSAR ML models	AChE	An ensemble learning model combining CatBoost and XGBoost, based on QSAR	Four drugs (phenserine, physostigmine, velnacrine, ipidacrine) supported by literature evidence	128
3D-QSAR deep neural network	BACE1	A deep neural network model integrating both structure-based and ligand-based features.	Fifth place in BACE prediction in the D3R grand challenge 4.	129
3D-QSAR deep neural network	BACE1	The descriptor space includes binary molecular fingerprints, 1D and 2D descriptors, and advanced 3D molecular fields requiring aligned chemical scaffolds in a unified space.	Qualitative classification achieved ~70% accuracy, while quantitative IC_{50} predictions had an RMSE of ~1 log.	130
3D-QSAR	AChE	3D-QSAR modeling was conducted for inhibitory activity using a 3D-fingerprint descriptor to encode protein-ligand interactions.	External validation results demonstrated strong performance with $n = 26$, $R^2 = 0.89$, and an MAE of 0.38 log units.	131
MathDL	BACE1	Advanced mathematics encodes high-dimensional interactions into low-dimensional representations, integrated with GANs for pose prediction and CNNs for energy evaluation.	Top place in BACE prediction in the D3R grand challenge 4 phase I.	132
Bipartite graph neural network	BACE1	A bipartite graph neural network combined with transfer learning was used for affinity prediction.	Top 9% results in BACE prediction in the D3R grand challenge 4 phase II.	133

Table 3 (*continued*)

Model	Target	Approach description	Result	Ref.
ADMET optimization				
LightBBB	Delirium AD	A ML model utilizing the light gradient boosting machine algorithm was developed for BBB prediction.	The model achieved an overall accuracy of 89%, an AUC of 0.93, a specificity of 0.77, and a sensitivity of 0.93.	189
Deep-B3	Delirium AD	Molecular descriptors, fingerprints, molecular graphs, and SMILES text notation were used for BBB prediction.	Deep-B3 (raw) achieved 95% sensitivity (SN), 41% specificity (SP), 0.41 MCC, 0.66 accuracy (ACC), and 0.80 AUC.	191

ADMET: absorption, distribution, metabolism, excretion, and toxicity; BBB: blood−brain barrier; DL: deep learning; DRIAD: Drug Repurposing in Alzheimer's Disease; GANs: generative adversarial networks; LBVS: ligand-based virtual screening; ML: machine learning; NETTAG: Network Topology-Based Deep Learning for Drug Discovery; PPI: protein−protein interaction; QSAR: quantitative structure−activity relationship; SMILES: simplified molecular input line entry system; VS: virtual screening.

pharmacophore fingerprinting, and conformer fingerprinting, along with a pre-training process, to train a molecule representation model from a library of 19.9 million compounds for LBVS[42]. This molecular representation helped identify two potent mitophagy inducers, kaempferol and rhapontigenin[42], from a natural compound library for AD treatment. Subsequent testing in nematode and rodent models of AD demonstrated that these molecules significantly enhanced the survival and functionality of glutamatergic and cholinergic neurons[42]. Additionally, they were shown to reduce amyloid-β and tau pathologies and improve memory in the animal models[42]. LBVS approaches have been extensively explored for targets in AD, as shown in Table 4. These studies cover various targets, such as GSK3B, amyloid-beta peptide, 5-HT receptors, and BACE1. A range of methods, including ML, pharmacophore-based deep neural networks, and hybrid approaches, have been applied, demonstrating the broad applicability of LBVS in AD research[119,120,143,145,146].

Docking and molecular simulation are traditional and widely used methods in SBVS for drug discovery[121,162-164]. The main limitation of these approaches is the high computational cost, especially when screening large compound databases, and the need for accurate protein structures, which limits the accuracy of the screening outcomes. For instance, VirtualFlow[121], a highly automated and versatile open-source platform, has a perfect scaling behavior for screening ultra-large libraries. Based on VirtualFlow, they identified a nanomolar affinity inhibitor for KEAP1, a target for AD and delirium, from a library of 1.4 billion make-on-demand compounds[121]. Despite the successful discovery of hit compounds, it takes around 15 h using 160,000 CPUs to dock 1 billion compounds[121].

Recent developments in DL-based docking methods have demonstrated relatively faster speeds and better accuracy compared to traditional docking methods[144]. A Deep Docking platform has been introduced that speeds up the process by up to 100 times and significantly improves the identification of promising drug candidates compared to conventional computational methods[144]. The core of these DL-based docking methods are Compound Target Interactions (CTI)[165] prediction methods, which will be explained in detail later. Currently, there are limited studies focused on AD drug discovery using DL-based docking for SBVS, making this an interesting area that warrants further research.

4.2.2. De novo drug design

De novo drug design is another method that utilizes generative models to design hits or carry out lead optimization based on specific demands[56,122,123,150,166-177]. The generative models learn from the molecules within the training dataset, extract representative features and representations, and eventually generate new molecular structures with a high potential for better drug profiles in terms of bioactivity and other properties[55,166,167]. Compared with VS, *de novo* design can generate novel molecular structures and optimize the molecules with desirable properties. However, VS identifies in-stock compounds instead of novel structures, which minimizes the time and cost for compound synthesis. As an example, a recent study used generative AI to design a small-molecule TNIK inhibitor; in a randomized, double-blind, placebo-controlled phase I clinical trial, the new compound demonstrated safety and PK profiles comparable to existing treatments, showcasing the capabilities of the generative AI-driven drug discovery pipeline[168].

A wide range of DL models, including GAN[171,172], VAEs[169,170], RL[56,173], RNNs[174], GNNs[175], transformers[177], and diffusion models, such as RoseTTAFold All-Atom[150,176], have been developed for *de novo* drug design. The main differences among these models lie in their molecular representation approaches, generation methods, and validation techniques. The applications of these models have also increased from molecule generation based on reference molecules to Scaffold Hopping, or drug optimization and design of 3D ligands within the protein pocket directly[176,177].

A generative framework was proposed for designing inhibitors for BACE1, an enzyme implicated in Alzheimer's disease that has proven challenging to target effectively, with multiple existing clinical trial failures due to insufficient brain penetration and off-target effects[122]. Potential candidates need to demonstrate both good bioactivity for inhibiting BACE1 and good permeability through the BBB[122]. This framework utilizes a Wasserstein GAN with Gradient Penalty, which can generate new molecular structures using the generator and evaluate their bioactivity and BBB permeability using the discriminator[122]. This approach resulted in the generation of more than 1,000,000 new candidate inhibitors for BACE1 with optimal bioactivity and BBB properties[122].

Graph generative models were proposed to generate hits for JNK3 and GSK3B using substructures called molecular rationales, identified based on their contribution to properties of interest[123]. These models expand molecular fragments—referred to as 'rationales' in this context (key structural elements contributing to specific properties or biological activities)—into complete molecules. They compose these molecules as mixtures of multiple rational completions and are fine-tuned to maintain the desired properties[123]. This generative approach shows significant improvements in the accuracy, diversity, and novelty of generated compounds compared to state-of-the-art baselines in various drug design tasks[174].

Table 4 A summary of applications of AI in protein-based therapeutics for delirium and AD.

Model	Target	Approach description	Result	Ref.
Structure prediction				
AlphaFold2	Delirium AD	Based on DL and MSAs to predict 3D protein folding.	First place in CASP14, with over 85% GDT_TS backbone accuracy for complex protein structures.	60
EquiFold	Delirium AD	SE (3)-equivariant all-atom protein structure prediction model for faster and more accurate antibody prediction.	Achieves similar or better backbone atom RMSD for antibody prediction compared to AlphaFold-Multimer and IgFold, while being significantly faster.	147
DeepH3	Delirium AD	Employs DL to predict antibody H3 loop structures, critical for antigen binding.	DeepH3 reduced the average RMSD by 32.1% (1.4 Å) compared to Rosetta on the Rosetta antibody benchmark dataset.	148
ABLooper	Delirium AD	Utilizes ML and knowledge-based methods to model antibody CDR loops.	On the Rosetta antibody benchmark, ABlooper achieves an average CDR-H3 RMSD of 2.49 Å, which improves to 2.05 Å for its top 75% most confident predictions.	149
RoseTTAFold all-Atom	Delirium AD	A unified approach for structure prediction and design of assemblies involving proteins, nucleic acids, small molecules, metals, and chemical modifications.	The most accurate predictions in the CAMEO blind ligand-docking challenge were achieved for proteins with low sequence homology (BLAST *e*-value >1) and ligands with low similarity (Tanimoto similarity <0.5).	150
AlphaFold3	Delirium AD	Enables the prediction of joint structures for complexes, encompassing proteins, nucleic acids, small molecules, ions, and modified residues.	Achieves best performance in predicting structures of various complexes through time-series splitting.	59
Binding site prediction				
ProB-site	Delirium AD	The model generates three feature sets per amino acid from protein sequences, processes them with sub-CNNs, and classifies the combined features using fully connected layers.	ProB-site achieved 0.799 accuracy and 0.844 ARROC on the benchmark dataset, and on test_315, it yielded an MCC of 0.351 and AUPRC of 0.446.	151
EquiBind	Delirium AD	The SE (3)-equivariant geometric deep learning model enables direct prediction of a ligand's bound pose and orientation as well as receptor binding sites.	Improves over the baselines for predictions in the >4 Å regime for blind self-docking, while outperforming baselines in all metrics except the 25th percentile and the fraction of predictions with RMSD below 2 Å for blind re-docking.	152
TANKBind	Delirium AD	TANKBind is a trigonometry-aware neural network for binding prediction, using trigonometric constraints and segmenting the protein into functional blocks to target binding sites.	Compared to baselines, this model increases the fraction of predictions with ligand RMSD below 5 Å by 16% in re-docking, 22% in self-docking, and 42% in the more challenging new-protein setting.	153
EpiCluster	Delirium AD	Clustering-based approach for identifying common epitopes across multiple antigens.	EpiCluster outperforms previous methods, achieving an AUC of 0.89 and an MCC of 0.49 on the epitope3D benchmark set.	154
EpiDope	Delirium AD	DL-based approach to predict peptide sequences that can serve as epitopes.	EpiDope, with an area under the receiver operating characteristic curve of 0.67 ± 0.07, outperforms all current linear B-cell epitope prediction tools.	155
BepFAMN	Delirium AD	Uses ML to predict linear B-cell epitopes from protein sequences.	The performance on the testing dataset demonstrates notable improvements, achieving an accuracy of 78.27%, sensitivity of 81.87%, specificity of 74.75%, and an AUC of 0.7831.	156
De novo protein design				
FoldIt, Rosetta, ProteinMPNN, AlphaFold 2	Amyloid	FoldIt-designed proteins were enhanced with strands and helices. Rosetta optimized sequences, followed by interface redesign to improve affinity. ProteinMPNN refined surface residues, and AlphaFold2 validated designs for testing.	Nanomolar affinities to target peptides *in vitro* and in cells.	157

Table 4 (*continued*)

Model	Target	Approach description	Result	Ref.
Rosetta, RosettaRemodel, FastDesign, MotifGraft docking	Amyloid	Designed a library of miniproteins with an α-helix and 2−3 β-strands using Rosetta, optimized with RosettaRemodel and FastDesign. MotifGraft docking generated 1 million sequences ranked by binding energy, with stable designs confirmed by MD and validated *via* CD spectroscopy and denaturation studies.	ThT kinetics assays confirmed the inhibitors block primary amyloid aggregation, while biosensor cell assays showed they also inhibit secondary seeding, with varying effects between tau and αSyn inhibitors due to differences in aggregation pathways.	158
Fine-tuned Rfdiffusion, RoseTTAFold2, ProteinMPNN	IL-7Rα	Fine-tuned RFdiffusion and RoseTTAFold2 on antibody structures before *de novo* antibody design. CDR loops were designed with ProteinMPNN and refined using the fine-tuned RoseTTAFold2.	Nanomolar binding affinity of the antibodies was confirmed.	159
Rosetta, AlphaFold 2, MD	Tau	The tau oligomer-selective epitope 343KLDFK347 and designed a β-helical scaffold with multiple copies of the tau fragment (amino acids 339−354).	In SPR experiments, the β-helical scaffold bound tau epitope antibodies, indicating a tau oligomer-like conformation.	160
Protein optimization				
RF Classifier	IL-17A	Their "re-epitoping" strategy identifies antibodies with initial complementarity to a desired epitope. Using analyses of epitopes and paratopes, they predicted amino acid substitutions to enhance binding, generating small antibody libraries selected *via* ML.	X-ray crystallography confirmed that the designed antibody binds to the targeted epitope, and cell-based assays verified its functionality.	161

AUC: Area Under the ROC Curve; AUPRC: Area Under the Precision-Recall Curve; ARROC: Area under the Robust Receiver Operating Characteristic curve; BLAST: Basic Local Alignment Search Tool; CAMEO: Continuous Automated Model Evaluation; CASP14: Critical Assessment of protein Structure Prediction, Round 14; CDR: Complementarity-Determining Region; CDR-H3: The third hypervariable region of the heavy chain CDR; CNNs: Convolutional Neural Networks; DL: Deep Learning; GDT_TS: Global Distance Test - Total Score; IL-17A: Interleukin-17A; IL-7Rα: Interleukin-7 Receptor Alpha chain; ML: Machine Learning; MCC: Matthews Correlation Coefficient; MSAs: Multiple Sequence Alignments; ProteinMPNN: Protein Message Passing Neural Network; RMSD: Root Mean Square Deviation; SE(3)-equivariant: Special Euclidean Group in 3D equivariance; SPR: Surface Plasmon Resonance.

However, most *de novo* design work relies on *in silico* methods instead of wet lab experiments to validate the outcomes[56,122,123,150,166-177]. This is mainly because novel structures are difficult to synthesize. This limitation prevents proper assessment of the results in real-world scenarios for different DL approaches, thereby constraining the advancement of these models for AD and delirium drug discovery.

4.2.3. Drug repurposing

Drug repurposing, also known as drug repositioning, is a strategy in the biopharmaceutical industry that involves finding new therapeutic uses for existing drugs[178]. While the development of new drugs is typically costly and time-consuming, repurposing existing drugs not only accelerates the process but also benefits from previously-known safety profiles[179]. Effective therapies have been identified for many diseases through drug repurposing, including cancer and Parkinson's disease, demonstrating the effectiveness of this approach for drug discovery[180,181]. The Ballard et al.[182] study serves as an example of how a literature review combined with the Delphi consensus process can be employed to identify potential repurposed agents for AD. For example, memantine, initially developed as an anti-diabetic agent, has been repurposed for AD[183].

There are also multiple studies leveraging DL approaches for drug repurposing in AD[124-127,178,182,184,185]. Compared to traditional drug repurposing methods, which rely on human efforts to review literature and vote on results, DL provides a more effective approach. It can integrate structured biological contexts, such as pathways and networks, as well as analyze large-scale multi-omics datasets. By identifying potential targets, and recommending drugs based on drug-target network predictions[184], DL facilitates more effective drug repurposing by providing a comprehensive analysis of the diseases, leading to better identification of potential drug candidates[182,186].

As an example, a network topology-based DL framework (NETTAG)[124] has been presented, which integrates diverse molecular quantitative trait loci (QTLs) datasets, such as expression-QTL and histone-QTL, with the human PPI networks[124]. This approach identified over 150 AD-risk genes and numerous druggable targets, highlighting the framework's potential in uncovering disease mechanisms and advancing therapeutic development[185]. By leveraging network-based predictions and retrospective case−control analyses involving 10 million individuals, NETTAG identified four drugs (ibuprofen, gemfibrozil, cholecalciferol, and ceftriaxone) as being associated with a reduced risk of AD incidence. This work underscores the power of using DL to analyze various data sources to drive drug repurposing efforts[124].

Similarly, as mentioned, different studies have utilized various types of multi-omics data, such as genomics, transcriptomics, epigenetics, and drug-target networks, to identify potential drugs for AD[125-127]. These studies demonstrate the ability of DL to analyze complex datasets and generate drug repurposing results.

4.2.4. Compound-Target Interaction prediction

Compound-Target Interaction (CTI) prediction, also known as affinity or drug-target interaction prediction, involves forecasting the biochemical interaction between a compound and a specific biological target, usually a protein[165]. The compound binds to the target at a specific site, and the strength of this interaction,

determined by factors such as hydrogen bonding, hydrophobic interactions, and van der Waals forces, is referred to as affinity. Accurate CTI predictions help identify compounds that can modulate target protein activity, leading to therapeutic effects[187]. CTI prediction can serve as *in silico* assessment metrics for VS and *de novo* design, enabling the identification and optimization of compounds with better affinity for drug targets, ultimately improving the pharmacodynamics of drugs[188].

ML approaches have been developed for predicting CTIs[128,189-193]. Quantitative structure−activity relationship (QSAR) models, which predict compound properties from molecular structure, are widely used in CTI prediction for AD[128,189-193]. These models leverage molecular descriptors (numerical values for properties like hydrophobicity, electronic distribution, hydrogen bonding, and geometry) and apply statistical or ML techniques to predict how structural changes affect CTIs[55,189]. QSAR-based methods have been widely applied to develop CTI prediction models for various targets, including AChE, KEAP1, BACE1, and butyrylcholinesterase inhibitors, using techniques like ensemble learning and artificial neural networks, as shown in Table 4 [128,189-192]. Other studies have demonstrated that QSAR modeling can predict the CTIs of compounds against multiple different targets[191,193]. These studies underscore the wide application of QSAR modeling for CTI prediction in AD drug discovery.

However, these QSAR models rely solely on two-dimensional molecular descriptors without accounting for the three-dimensional spatial arrangement of the compound interacting with proteins[128,189-193]. This limitation results in a lack of robustness and generalizability in the prediction outcomes. To address this, some research integrates 3D-based descriptors, generated by docking programs, into the modeling process to incorporate three-dimensional information[129,131,194]. Researchers incorporate 3D information generated by Open Babel, Smina, 3D field-based descriptors, and molecular docking to improve prediction accuracy. This enhances prediction performance and has led to good results in competitions such as the Drug Design Data Resource Grand Challenge 4[129,131,194]. However, these 3D QSAR models also have a major drawback: inaccurate docking results can lead to inaccuracies in the 3D-based descriptors, resulting in false predictions[128,131,193].

Recent advances in DL models for predicting CTIs based on protein and compound representations provide alternative techniques with higher accuracy compared to docking and QSAR models[59,195]. AlphaFold 3[59], for example, uses multiple sequence alignments to identify residue pairs that co-mutate, indicating that these pairs are likely in proximity in 3D space[59]. It then employs a graph-based representation to link these residue pairs and predict a probable 3D structure, like AlphaFold 2[60]. Additionally, AlphaFold 3[59] includes a diffusion model that utilizes 'noised' atomic coordinates, which is beneficial for proteins with limited Multiple Sequence Alignment coverage, such as antibodies and novel proteins. It achieves significantly higher accuracy in predicting protein-ligand binding conformations (measured by more structures with less than 2 Ångströms deviation from experimental structures) compared to the best traditional docking program, Vina, when evaluated on PoseBusters, a standard benchmark dataset designed to assess the quality of molecular docking predictions[59]. Specifically, AlphaFold 3[59] shows a 37.9% higher percentage for PoseBusters V1 (89.2% *vs*. 52.3%) and a 33.5% higher percentage for PoseBusters V2 (93.2% *vs*. 59.7%)[59]. Other DL models, such as TransformerCPI, have been developed to improve the prediction accuracy of CTIs[195].

Researchers are also exploring similar methods for AD-related drug discovery[132,133]. For instance, MathDL[132] uses techniques such as differential geometry and algebraic topology to encode complex interactions into low-dimensional representations, excelling in pose prediction for BACE1 ligands, achieving the top position in pose prediction for BACE1 ligands in Stage 1a[132]. Another approach combines a bipartite GNNs with transfer learning—an algorithm that applies knowledge gained from one problem to help solve related problems—creating representations of both drug molecules and protein binding sites. This method outperformed the leading competitor by 9% when predicting interactions with the BACE1 target[133]. These studies highlight the potential of DL to predict compound−target interactions directly from protein and compound inputs.

4.2.5. ADMET optimization

Optimization of Absorption, Distribution, Metabolism, and Excretion-Toxcitity (ADMET) properties is critical in drug discovery as it affects a drug's efficacy, safety, and clinical success[196]. Early assessment and optimization of these PK properties help reduce late-stage failures and associated costs[196]. Computational approaches offer a fast, cost−effective way to focus on candidates with better ADMET potential, thereby minimizing the need for labor-intensive wet-lab experiments[197]. These computational ADMET prediction and optimization methods enable rapid screening, predictive modeling, integration with experimental data, and iterative optimization of lead compounds, ultimately enhancing the efficiency and success rate of drug development.

ADMET prediction has evolved significantly, but started with rule-based methods based on expert summarization. For instance, Lipinski's Rule of Five[198], formulated by Christopher A. Lipinski in 1997, is a set of guidelines for evaluating the drug-likeness of a compound, particularly its potential as an orally active drug in humans[199]. Another widely used expert system is Derek for Toxicity[200], which predicts potential toxicological endpoints based on structural alerts—specific chemical substructures or patterns associated with known toxic effects[200,201]. By analyzing the structural features of a compound, Derek can provide early warning signs of potential toxicity, aiding researchers in the drug development process and helping to prioritize safer compounds for further testing[201]. However, rule-based methods for ADMET prediction are limited by their static nature, often excluding promising compounds and including toxic ones due to their inability to cover the complex and diverse chemical space.

Recent developments in QSAR-based approaches and DL models provide improved methods for automatically learning complex patterns from large datasets, leading to more accurate predictions of ADMET properties[65,101,202-207]. These advanced models can analyze vast amounts of data to uncover intricate relationships between molecular structures and their PK and toxicological profiles. Similar to CTIs, ADMET prediction can also leverage ML algorithms to analyze descriptors, as seen in 2D QSAR models[128]. For DL approaches, various methods have been developed for ADMET prediction, such as MPNN[65,202], GNNs[203-205], and graph transformers[186,206,207].

Additionally, there are multiple online platforms for ADMET prediction based on DL approaches[208-213]. ADMETLab 3.0[208] is a web server that employs a multi-task Directed MPNN architecture, enabling the prediction of over 119 ADMET endpoints[208]. Similarly, platforms such as ADMET-boost, admetSAR 2.0, SwissADME FAF-Drugs4, vNN-ADMET, and pkCSM provide accessible online tools for *in silico* ADMET prediction,

streamlining the drug discovery process by offering rapid and reliable computational assessments[209-213].

For AD and delirium drug discovery, effective drugs need to cross the BBB to reach their targets in the central nervous system[196]. To properly assess the BBB permeability of a compound, a dataset of 7162 compounds with BBB permeability data was constructed using information compiled from the literature[134]. Authors then trained a ML model based on the Light Gradient Boosting Machine algorithm (a decision-tree based algorithm that efficiently handles large datasets and delivers fast and accurate predictions)[214] and achieved an overall accuracy of 89% for predicting BBB permeability[134]. Similarly, another DL-based multimodel framework, Deep-B3, which includes molecular descriptors and fingerprints, molecular graphs, and SMILES text notation as feature inputs has been developed to predict BBB permeability[135]. The online web server for Deep-B3 is available at http://cbcb.cdutcm.edu.cn/deepb3/ for free access[135]. Many other DL-based approaches to predict BBB permeability exist, including RNNs[215], GCNs[216], and attentive GNNs[215].

In addition, drug dosing and administration can be optimized using AI for delirium and AD. For instance, RL has been applied to identify the best dosing for dexmedetomidine in delirium patients, optimizing clinical outcomes to prevent delirium in intensive care unit patients[217,218].

4.3. Protein-based therapeutics

Protein-based therapeutics encompass categories such as protein or peptides (short chains of amino acids used for signaling or as hormones), antibodies (immune proteins designed to target specific antigens), and other therapeutic proteins such as enzymes and cytokines that modulate biological processes[219]. Protein-based therapeutics have shown promising results in clinical trials for AD treatment, slowing disease progression and improving cognitive function[219,220].

Recently, the US FDA approved lecanemab[221], an IgG1 monoclonal antibody, for AD treatment. An 18-month, multicentre, double-blind Phase III clinical trial demonstrated that lecanemab reduced amyloid markers in early AD and led to a small but significant deceleration of cognitive and functional decline compared to placebo, although it was associated with severe adverse events[222]. Additionally, other antibodies like donanemab and remternetug have shown promising results in Phase III trials for reducing amyloid markers[223], with donanemab approved by the FDA on July 2, 2024[224].

The discovery of protein-based therapeutics such as antibodies has traditionally relied on experimental methods such as directed evolution[225] and animal immunization[219,225]. However, these approaches are time-consuming, labor-intensive, and face challenges in targeting epitopes and scaling antibody production[226]. Recent developments in various AI predictive modeling approaches, such as AlphaFold for structure prediction[59,60], ProteinMPNN for protein sequence design[227], and ESM3 as a generative foundation model[70], offer alternative methods by applying computational and AI-based techniques to protein design with desirable functions[228,229]. This section will focus on discussing the applications of AI in the development of protein-based therapeutics for AD and delirium (Table 4).

4.3.1. Structure and binding site prediction

Understanding a protein's structure is crucial for rational protein design, as even minor mutations in its sequence can lead to structural changes that significantly affect various characteristics of the drug, such as binding affinity, specificity, and stability[220]. However, determining accurate protein structures is a lengthy and costly process, posing one of the major obstacles to rational drug design for protein-based therapeutics[230]. Traditionally, protein structures have been predicted computationally through physics-based modeling techniques like molecular dynamics (MD) simulations[231], homology-based modeling[232], or hybrid approaches such as MODELLER[233]. However, these methods rely on known structural information, are computationally intensive, and have limitations in their scoring functions[234].

AlphaFold 2, a ML-based model released in 2020, represents a significant breakthrough in protein structure prediction[56]. It won first place in the 14th Critical Assessment of Structure Prediction—a global community-wide experiment to evaluate the state of the art in protein structure prediction—achieving high backbone accuracy (with GDT_TS values exceeding 85%) even for complex protein structures[235]. Additionally, DL models such as EquiFold[217], DeepH3[148], and ABLooper[149] have been developed to predict specific protein structures like antibodies, addressing challenges such as the diverse conformations of antibody complementarity-determining regions, which can result in low prediction accuracy. Recently, DL approaches like RoseTTAFold All-Atom[150] and AlphaFold 3[59] have extended prediction capabilities for joint structures of complexes, including proteins, nucleic acids, small molecules, ions, and modified residues. This broadens the application of these models in biological studies and drug design.

In addition to protein structure prediction, identifying potential protein binding sites is vital for drug design and optimization[151-156,236]. Several computational methods have been developed to predict and analyze these binding sites. Tools like ProB-Site[151], EquiBind[152], DiffDock[236] and TANKBind[153] are designed to predict and examine the protein binding sites critical for drug interaction. For more specialized tasks such as epitope and paratope prediction in antibodies, methods like EpiCluster[154], EpiDope[155], and BepFAMN[156] have been developed to provide specific insights, enhancing the precision of antibody design. These tools help address the complexities involved in predicting binding interactions, ultimately improving the efficacy of therapeutic interventions.

Overall, recent developments in DL modeling allow for more accurate predictions of protein structure based on sequence data. This has become an important procedure for protein-based therapeutic discovery. Additionally, the representation component of structure prediction models has been used for developing protein design models. Despite the fact that errors may occur with complex proteins and flexible regions, these structure prediction approaches are becoming increasingly important and are widely applied in modern protein therapeutic discovery[237].

4.3.2. De novo protein design

Protein *de novo* design refers to the process of creating new protein structures and sequences entirely from scratch, without using templates from existing natural proteins[238]. The goal is to engineer proteins with specific structures and functions that don't naturally exist. For example, Rosetta Design[239] is a well-known suite of computational tools for protein design. It uses an energy minimization approach to predict and optimize protein structures, with algorithms for tasks such as sequence redesign, protein docking, and *de novo* design. However, these traditional methods are often limited because they rely on modifying existing proteins, which constrains their application[237,238].

Recently, several generative AI methods for *de novo* protein design have emerged, such as ProteinMPNN[227] and Rosetta Diffusion[240]. These advanced computational approaches use DL models, including diffusion models, language models, and VAEs, to directly generate protein structures without needing specific templates[227,240]. By leveraging vast amounts of protein structure and sequence data through pretraining, these generative models are able to create entirely new sequences or structures[227,240].

De novo-designed scaffolds with deep peptide-binding clefts were used to prevent amyloid fibril formation by targeting amyloidogenic sequences like Aβ42, tau, and serum amyloid A1[157]. Researchers leveraged the peptides' tendency to form β-strands, designing scaffolds with a central β-strand and α-helices. Using Rosetta[241] for sequence optimization and AlphaFold2[60] for validation, they refined the binders for high affinity through hydrophobic interactions[157]. The binders inhibited Aβ42 fibril formation *in vitro* and in cells, showing nanomolar affinities comparable to antibodies like aducanumab, and blocked secondary nucleation sites, offering tools for studying amyloid species[157].

Inhibitors were designed to prevent amyloid fibril growth by capping their ends[158]. Using Rosetta, authors created a library of miniproteins (35−48 amino acids) with α-helices and β-strands, optimized for binding energy and stability[158]. Docking *via* the MotifGraft protocol and MD identified stable designs, which were validated through circular dichroism spectroscopy and denaturation studies[158]. Thioflavin T kinetics assays confirmed that the inhibitors block amyloid aggregation, and biosensor assays showed inhibition of secondary seeding, with distinct effects for tau and αSyn due to differences in their aggregation pathways[158].

De novo-designed VHH antibodies, variable domains of heavy chain-only antibodies, also known as nanobodies (small, single-domain antibody fragments), targeting specific epitopes were developed using a fine-tuned RF diffusion network[159]. RFdiffusion and RoseTTAFold2 were fine-tuned on antibody structures, designing complementarity-determining regions loops witSh ProteinMPNN and refining them further with RoseTTAFold2[159]. Using a humanized VHH framework, researchers created antibodies targeting interleukin-7 receptor alpha, a potential target for AD[159]. The designed antibodies showed nanomolar-level binding affinity, highlighting the potential of *de novo* antibody design for treating these conditions[159].

De novo design weas applied to develop a novel cyclic peptide that resembles toxic tau aggregates, providing an improved platform for evaluating potential therapeutic antibodies in Alzheimer's disease research[242]. Authors incorporated multiple copies of the tau fragment (339−354) into a β-helical scaffold[242]. Surface plasmon resonance experiments showed the scaffold effectively bound tau-specific antibodies, closely mimicking the conformation of toxic tau oligomers[242]. The scaffold's ability to mimic oligomer conformation suggests it could serve as an effective immunogen and supports the use of *de novo* protein design for both drug development and *in vitro* assay creation for screening[242].

Overall, while the development of *de novo* protein design using generative models is still relatively new, there is already substantial research highlighting their potential in protein drug discovery. Future studies may explore combining generative protein design models with MD simulations, docking, and other computational methods to further accelerate protein drug design for conditions such as AD and delirium.

4.3.3. Protein optimization

As mentioned earlier, the discovery of protein-based therapeutics, particularly antibodies, has traditionally relied on animal immunization[219]. Consequently, various computational approaches have been developed to further optimize natural proteins by improving factors such as binding specificity and affinity, reducing immunogenicity, preventing aggregation, increasing bioavailability, decreasing molecular weight, solubility, aggregation propensity, and extending half-life[157,158,243-246]. These protein properties are important for the clinical success of protein drugs. For example, antibody therapeutics can aggregate, which may result in precipitation and a reduced shelf life before administration[247]. Additionally, aggregation within the body can increase the drug's immunogenicity, potentially triggering unwanted immune responses[248]. As a result, different data modeling approaches have been established to predict these properties and enable better selection of protein candidates with the most optimal properties.

An antibody for interleukin-17 receptor alpha, a potential target for AD, was optimized to enhance selectivity and affinity[161] using a "re-epitoping" strategy. This strategy is a sophisticated approach to antibody engineering that begins with identifying antibodies possessing initial complementarity—such as similar shape or charge—to a desired epitope, even if their original binding target is unrelated[161]. By utilizing knowledge-driven and physicochemical analyses of thousands of epitopes and paratopes, amino acid substitutions were strategically predicted to enhance complementarity[161]. Small libraries of antibody variants were subsequently created and screened *in silico* for binding affinity to the novel target protein, guided by a ML algorithm[161]. The structural accuracy of the designed antibody binding to the targeted epitope was confirmed through X-ray crystallography, while cell-based assays validated its functional efficacy[161].

There are various methods to enhance the drug-likeness of protein-based therapeutics, such as reducing immunogenicity, preventing aggregation, lowering viscosity, and extending the protein's half-life [157-159,249-253]. For instance, tools like ProteinMPNN[227] can assist in refining surface residues for crystallization and humanization, helping reduce immunogenicity[157,158]. Additionally, solubility and aggregation prediction tools like Camsol[249], SOLart[250], and AGGRESCAN 3D[251], as well as humanization tools such as Hu-mAb[252], and BioPhi[253], provide valuable insights into optimizing protein properties. However, the application of these models for improving protein drug properties related to AD and delirium remains limited, necessitating further studies.

4.4. Biomarker discovery and disease diagnosis

Biomarkers are used to evaluate disease risk, confirm diagnoses, or predict progression as measurable indicators of biological processes, disease activity, or treatment responses[254]. Research in dementia and delirium has explored a wide range of biomarkers across various biological domains, including genetics, gene expression, proteins, metabolism, neuroimaging, electrophysiology, gut microbiota, sleep patterns, gait, and digital measures[255-264].

Metabolomic biomarkers have been shown to enhance the understanding of postoperative delirium pathogenesis[264]. By applying ML algorithms such as XGBoost (eXtreme Gradient Boosting)[265] and denoising autoencoders[266,267], researchers successfully identified potential primary and secondary markers from

serum samples, highlighting the potential of ML in discovering delirium biomarkers[264].

Neuroimaging biomarkers, such as MRI or PET scans, can reveal structural or functional changes in the brain, while protein-based biomarkers in blood or cerebrospinal fluid can detect abnormal levels of amyloid or tau associated with neurodegenerative conditions[259,262,263]. Digital tools, including wearable devices, mobile apps, and sensors, provide continuous, real-world monitoring, capturing biomarkers related to movement, sleep, heart rate variability, and cognitive function[260,268]. ML models can then integrate this diverse information, identifying patterns within complex datasets and predicting disease outcomes or treatment responses with greater precision, an area where traditional statistical analysis methods often face challenges[101]. Furthermore, AI can facilitate biomarker discovery by enabling the molecular subtyping of dementia and potentially uncovering relationships between complex conditions such as delirium and AD[269-271].

Researchers have developed effective data representation approaches for these different data modalities, allowing for the identification of hidden relationships between biomarkers and diseases. In addition, AI models such as RNNs are well-suited for analyzing time-series data, providing an effective method for studying disease progression[272,273].

However, challenges remain regarding the availability of high-quality patient data, particularly related to data heterogeneity, patient data security, and trust in AI. Data collected from various sources, such as neuroimaging, digital tools, and molecular assays, can differ significantly in format, scale, and quality, creating challenges for harmonization and integration[274]. Additionally, ensuring patient data security and privacy is crucial, as sensitive health information must be protected to comply with ethical standards and regulations. Furthermore, building trust in AI models used for biomarker discovery and disease prediction requires transparency in how these models process data, make decisions, and address biases. Addressing these factors is key to advancing AI-driven research in dementia and delirium while maintaining the ethical use of patient data[275].

5. Discussion

Delirium and AD share common challenges in drug discovery. Biologically, our understanding of their mechanisms remains incomplete, and reliable animal models, especially for delirium, are lacking[1]. Chemically, designing drugs that effectively bind to their targets and cross the BBB is difficult[134,135,196,215,216]. Clinically, patient heterogeneity and a lack of robust biomarkers complicate confirmation of target engagement and treatment efficacy[43,44]. While AD research has benefited from established biomarkers[276], delirium remains in need of similar advancements. Despite the significant progress in AI-driven drug discovery for AD, these approaches have not been extended to research into delirium where they could be useful given the shared challenges.

AI holds promise for addressing these challenges by enhancing target identification, compound screening, and drug repurposing. For instance, AI-assisted multi-omics analysis can uncover novel targets in both conditions[96,97,264], and models trained on BBB permeability data can help identify candidate compounds that reach the brain[134,135,196,215,216]. In addition, deep neural network-based AI methods can enable drug repurposing studies exploring shared potential drug candidates between delirium and AD, informed by a deeper understanding of these diseases' connections[130,132-137]. These tools, along with other ML and computational approaches, can accelerate the discovery and optimization of therapeutics for these complex neurodegenerative disorders. However, several key barriers remain.

5.1. Data limitations and quality

Despite concerted efforts to establish large AD and general drug discovery databases, high-quality data that allow the development of more accurate predictive models are still missing[196]. High-quality data refers to information that is accurate, complete, and systematically collected, minimizing errors such as missing data, misdiagnoses, and inconsistencies in assessment methods. This issue is even more pronounced in delirium research, where collecting high-quality, standardized data from patients experiencing delirium is inherently difficult[31-34]. In population-based cohorts[34], reliable baseline dementia status data can be obtained, but delirium status is often extracted from hospital records, which may lead to a high number of false negatives. A recent Norwegian study found a ninefold increase in identified delirium cases when all case notes were thoroughly reviewed compared to discharge records alone[11]. Conversely, studies including acutely admitted patients[31] benefit from bedside assessments ensuring high-quality delirium data, but dementia status before inclusion must rely on hospital records, information from relatives, and care home documentation, sources that are known to underreport cases. For instance, in Norway, only 30% of dementia patients have a formal diagnosis[103]. Only recently have studies emerged that incorporate both high-quality baseline dementia assessments and robust delirium data from bedside evaluations[277,278].

Moreover, the datasets are relatively small in scale and often require further cleaning and standardization. For instance, binding affinity experimental data for AD-related targets are typically limited to a few thousand entries, which constrains the ability to achieve high accuracy in binding prediction models using DL approaches[131,133,190]. As another example, many predictive models for BBB permeability are built using the BBBP dataset from the public MoleculeNet repository[279]. However, this public dataset includes records sourced from various public data sources, which often contain errors, such as contradictory results for the same compounds, as well as inaccuracies in SMILES strings and molecular properties like chirality. These errors introduce noise and inconsistencies into the predictive models, negatively impacting their accuracy and reliability for predicting BBB permeability, which is critical for AD and delirium drug design.

5.2. Disease heterogeneity and dynamic nature

Both AD and delirium are highly heterogeneous[1,2,14-16], which challenges the development of AI models that generalize across diverse patient populations. For instance, models trained on mixed subtypes, such as hypoactive and hyperactive delirium, may overlook the distinct features of each, limiting their utility for targeted therapy development. Similarly, AD presents with diverse phenotypes and variable disease progression, particularly in younger patients. In addition, delirium's onset may be rapid, and symptoms may change dramatically over short periods[7,8]. This makes data collection and modeling extremely challenging. Traditional AI models often assume static data, but delirium requires approaches that can handle temporal dynamics and rapid changes.

5.3. Gaps in experimental validation

In addition, a major limitation in current AI drug discovery studies for AD and delirium is the lack of direct validation in relevant animal models, as studies often rely on affinity experiments or *in silico* simulations rather than complex *in vivo* experiments that provide more clinically translatable results[56,119,120,122,123,128,143-146,150,166-177,189-193]. This challenge arises because existing animal models only partially mimic the complex pathology and heterogeneity of human AD and delirium, limiting their effectiveness in capturing the full scope of these diseases[280,281]. Additionally, the high costs and lengthy timelines of clinical trials further hinder comprehensive validation efforts[39,40]. As a result, bridging this gap requires a collaborative effort among AI experts, clinical researchers, and organizations to develop improved methods for preclinical validation that better reflect human disease, as well as AI-driven strategies for optimizing clinical trial design, identifying more sensitive outcome measures, and even predicting individual patient responses to treatment.

5.4. Leveraging emerging AI tools

The breakthroughs in the AI field can be actively explored further to tackle the afore-mentioned challenges. For instance, the recent development of large language models enables more effective data cleaning approaches, improving the quality and quantity of data related to delirium and AD, though this raises significant privacy concerns and regulatory challenges under data protection frameworks like GDPR[282]. New ADMET-related datasets, such as PharmaBench[196], have utilized large language models for data cleaning, demonstrating the potential of applying these AI advancements to enhance drug discovery efforts. This showcases the possibility of leveraging recent AI breakthroughs to address data-related issues and accelerate progress in the drug discovery field.

The field of AI has grown rapidly, allowing researchers to better understand the features learned by AI models[275,283]. This should be encouraged in the context of delirium and AD research to provide deeper insights into model predictions and enhance trust in AI-driven findings. Moreover, AI can be integrated with other computational approaches, such as physics-based methods[284,285] to further enhance accuracy and efficiency in drug discovery. These combined approaches could lead to more powerful predictive models and innovative solutions for complex neurodegenerative diseases.

5.5. Combination therapy and synergistic design

In addition, given the limitations of monotherapies in treating the complex and multifaceted nature of AD and delirium, combination therapies, guided by AI, represent a promising avenue for future research. ML models, particularly network-based approaches and those trained on large datasets of drug−drug interactions, molecular pathways, and clinical outcomes, can predict synergistic drug combinations[186,286,287]. These models can also help optimize dosing regimens to maximize therapeutic effects while minimizing adverse reactions[286,287]. For example, while not discovered through AI, the combination therapy involving memantine and cholinesterase inhibitors for dementia highlights the potential benefits of multi-drug approaches in AD[288]. By leveraging AI's ability to analyze complex datasets and predict drug interactions, researchers can accelerate the discovery of effective combination therapies for both AD and delirium, addressing a critical need in the treatment of these devastating conditions.

5.6. Real-world applications and progress

Recent advances[289] in AI-driven drug discovery have led to significant milestones in clinical trials. Since 2015, 75 AI-discovered molecules have entered clinical trials, with 67 still ongoing as of 2023[289]. These molecules have demonstrated impressive success rates, with 80%−90% advancing through Phase I and approximately 40% progressing to Phase II. Notably, failures in Phase I were predominantly due to factors such as insufficient funding, strategic shifts in company priorities, or changes in the competitive landscape, rather than deficiencies in meeting the scientific evaluation criteria. Much of this early success can be attributed to a focus on well-validated biological targets. By targeting pathways and mechanisms already known to be involved in disease, researchers minimize the risk of failure due to unexpected biological effects[289]. At the same time, the statistics of AI-discovered molecules that have not gone through the clinical stage cannot be accurately calculated due to limited data[290]. In the realm of Alzheimer's research, Exscientia's development of DSP-0038, a dual-targeted 5-HT1A agonist and 5-HT2A antagonist designed to tackle AD psychosis, provides a concrete example of AI's application[291].

5.7. The path forward: interdisciplinary collaboration

The successful applications of AI in drug discovery for AD and delirium require close collaborations between experts from multiple disciplines, including molecular neuroscience, neurology, pharmacology, bioinformatics, computer science, and others. While AI can efficiently analyze complex biological data and predict potential drug candidates[292,293], its effectiveness depends on domain knowledge to ensure biological relevance and clinical feasibility[117,294]. Interdisciplinary teams can address AI's limitations by refining model interpretability, improving data quality through curated biomedical datasets[295], and integrating experimental validation with computational predictions[42]. Strengthening collaboration across these fields will be essential for successfully translating AI-driven discoveries into clinically viable therapeutics.

Overall, with the advancement of modeling approaches, the growing availability of data, and improvements in hardware, AI is expected to become increasingly applicable and significantly enhance the drug discovery process for delirium and AD.

6. Conclusions

In summary, AI has already demonstrated its transformative potential in drug discovery for delirium and AD, ranging from identifying novel therapeutic targets to optimizing drug design. While challenges remain in data quality and model interpretability, ongoing advancements in AI methodologies, data cleaning techniques, and hardware capabilities promise to further accelerate the drug discovery process. As AI continues to evolve, it is expected to significantly contribute to the development of more effective therapies for these two brain diseases, as well as other complex neurodegenerative conditions.

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Author contributions

Ruixue Ai and Xianglu Xiao contributed to Conceptualization. Ruixue Ai, Xianglu Xiao, and Shenlong Deng contributed to Writing (original draft). All authors contributed to writing (Review & Editing). Guang Yang and Evandro Fei Fang contributed to supervision, project administration, and funding acquisition.

Conflicts of interest

Evandro Fei Fang is a co-owner of Fang-S Consultation AS (Organization number 931,410,717) and NO-Age AS (Organization number 933 219 127); he has an MTA with LMITO Therapeutics Inc (South Korea), a CRADA arrangement with ChromaDex (USA), a commercialization agreement with Molecule AG/VITADAO, and MTAs with GeneHarbor (Hong Kong, China) Biotechnologies Limited and Hong Kong Longevity Science Laboratory (Hong Kong, China); he is a consultant to MindRank AI (China), NYO3 (Norway), AgeLab (Vitality Nordic AS, Norway), and Hong Kong Longevity Science Laboratory (Hong Kong, China). Geir Selbæk has received honoraria for giving lectures to Eisai and Eli-Lilly and participated in advisory boards for Eisai, Roche and Eli-Lilly concerning disease-modifying treatments of Alzheimer's disease. David C. Rubinsztein is a consultant for Aladdin Healthcare Technologies Ltd., Mindrank AI, Nido Biosciences, Retro Biosciences, Drishti Discoveries, Carlyle Investment Management LLC, Alexion Pharma International Operations Limited, and PAQ Therapeutics.

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