The Journal of Prevention of Alzheimer's Disease 12 (2025) 100366

Contents lists available at ScienceDirect

The Journal of Prevention of Alzheimer's Disease

journal homepage: www.elsevier.com/locate/tjpad

Review

The role for artificial intelligence in identifying combination therapies for Alzheimer's disease

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ARTICLE INFO

Keywords:
Alzheimer's disease (AD)
Artificial Intelligence (AI)
Drug Combination
Endophenotype

ABSTRACT

Despite substantial investment in biomedical and pharmaceutical research over the past two decades, the global prevalence of Alzheimer's disease (AD) and AD-related dementias (AD/ADRD) is still rising. This underscores the significant unmet need for identifying effective disease-modifying therapies. Here, we provide a critical perspective on the application of data science and artificial intelligence (AI) to the rational design of drug combinations in AD and ADRD, addressing their potential to transform therapeutic development. We examine AI's current and prospective capabilities in therapeutic discovery, identify areas where AI-driven strategies can enhance drug combination development, and outline how multidisciplinary professionals in the field, including clinical trialists, neuropsychiatrists, pharmacologists, medicinal chemists, and computational scientists, can leverage these tools to address therapeutic gaps. We also highlight AI's role in synthesizing the rapidly growing amount of biomedical data in the field of AD/ADRD, especially clinical trials, biomarkers, multi-omics data (genomics, transcriptomics, proteomics, metabolomics, interactomics, and radiomics), and real-world patient data. We further explore AI's utility in prioritizing potential drug combination regimens and estimating clinical effect size in combination therapy trials for AD/ADRD. Lastly, we emphasize AI-powered network medicine methodologies for prioritizing drug combinations targeting AD/ADRD co-pathologies and summarize the challenges of their translation to clinical practice.

1. Introduction

Alzheimer's disease (AD) and AD-related dementia (AD/ADRD) represent a major global health challenge, affecting millions of people worldwide. In the United States alone, an estimated 7 million people are living with (AD), a number projected to reach nearly 13 million by 2050 [1]. Globally, the impact is even more stark, with over 50 million people afflicted, a number expected to rise to 152 million globally by 2050 due to our rapidly aging population [2]. Although Lecanemab [3] and Donanemab [4] were approved by the U.S. Food and Drug Administration (FDA) for AD, the clinical efficacy of disease-modifying drugs needs improvement [5]. These challenges highlight the urgent need for continued research to develop effective treatments (such as drug combination therapies), to identify preventative measures, or to cure AD/ADRD.

Drug combination therapy, defined as administering 2 or more drugs

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https://doi.org/10.1016/j.tjpad.2025.100366
Received 9 July 2025; Received in revised form 28 August 2025; Accepted 2 September 2025
Available online 27 October 2025

concurrently to address one disease, can offer increased therapeutic efficacy. Determining drug combinations for AD/ADRD is challenging due to both the multifactorial nature of AD and the large number of potential drug combinations to be evaluated. In this regard, artificial intelligence (AI) has emerged as a powerful tool to identify and prioritize drug combinations through modelling the complex interactions between drug targets and disease biology, as well as integration of multimodal biomedical data (Fig. 1).

2. Drug combinations currently in the AD drug development pipeline

As of January 2025 [6], 30 pharmacological drug combinations from 53 CE interventional clinical trials registered on clinicaltrials.gov have been evaluated since 2015 (Table 1). Sixteen of these combinations were from completed, terminated, and withdrawn trials, and are thus not being currently evaluated. These combinations are (1) albumin + immunoglobulin, (2) baclofen + acamprosate (PXT864), (3) cromoglicic acid + ibuprofen (ALZT-OP1), (4) CST-2032 + CST-107, (5) dextromethorphan + quinidine (AVP-786), (6) donanemab + LY3202626, (7) donepezil + mefloquine (THN201), (8) donepezil + memantine, (9) donepezil + solifenacin (CPC-201), (10) insulin + empagliflozin, (11) losartan + amlodipine, (12) LY3202626 + itraconazole, (13) MK-1708 + itraconazole, (14) sabirnetug + rHuPH20, (15) simvastatin + *l*-Arginine + Sapropterin, and (16) and tauroursodeoxycholic acid + phenylbutyric acid (AMX0035). The failures of these 16 drug combinations are indicative of the challenges inherent in the development of combination therapeutics for AD in clinical trials.

Currently, there are ten drug combinations in ongoing trials, defined as 'recruiting', 'active, not recruiting', 'enrolling by invitation', and 'not yet recruiting.' These include (1) ciprofloxacin + celecoxib (PrimeC), (2) DAOIB + AO, (3) dasatinib + quercetin (*D* + *Q*), (4) dextromethorphan + bupropion (AXS-05), (5) E2814 + lecanemab, (6) polypill, rotigotine + rivastigmine, (7) resveratrol + quercetin + curcumin (RQC), and (8) wujia yizhi, xanomeline + trospium (KarXT). There are also an additional four drug combinations of unknown trial status: (1) dronabinol + palmitoylethanolamide (SCI-110), (2) sodium oligomannate (GV-971) + memantine, (3) STA-1 + donepezil, and (4) Tdap vaccine. In terms of phase, only sodium oligomannate + memantine is in Phase 4 trial, while all others are in Phase 1, 2, and 3 trials. A total of 5424 participants have thus far been involved in completed trials for drug combinations, while ongoing trials will enroll a total of 4205 participants.

In terms of the types of drug combinations, dextromethorphan + quinidine and dextromethorphan + bupropion are pharmacokinetic combinations (quinidine and bupropion inhibit CYP2D6 to prolong the half-life of dextromethorphan in plasma). The xanomeline + trospium combination is for side effect mitigation (cholinergic agonist xanomeline paired with peripheral cholinergic antagonist trospium). All others are pharmacodynamic combinations (combination vaccines, multitarget agents, etc.) with overall diverse mechanisms-of-action.

Among these drug combinations, donepezil + memantine was previously shown to confer cognitive benefit in moderate or severe AD patients [7,8]. Rivastigmine + memantine was shown to be well tolerated and also potentially beneficial [9,10], and cholinesterase inhibitors (donepezil, rivastigmine or galantamine) plus memantine have been frequently used as comparators or standard of care in the last two decades. Other combinations have failed to show clinically beneficial effects for AD patients or are still awaiting more participants and data. The lack of promising AD drug combinations presents both challenges and opportunities. In this regard, the recent advances of AI, multi-omics, and systems biology approaches provide powerful tools for the systematic identification of drug combinations for AD/ADRD.

3. Big data for Alzheimer's disease drug development

Open big data is a critical resource for AD drug development [11]. The AD Knowledge Portal [12], for example, is a multi-omics repository of over 243,000 datasets and analytical results as of May 2025. Agora (https://agora.adknowledgeportal.org) by AD Knowledge Portal provides interactive multi-omic (transcriptomic, proteomic, and metabolomic) data exploration for over 900 CE drug targets that have been nominated from AMP-AD and TREAT-AD, while AlzTarget (https://alztarget.org) is a multi-omics database for AD target

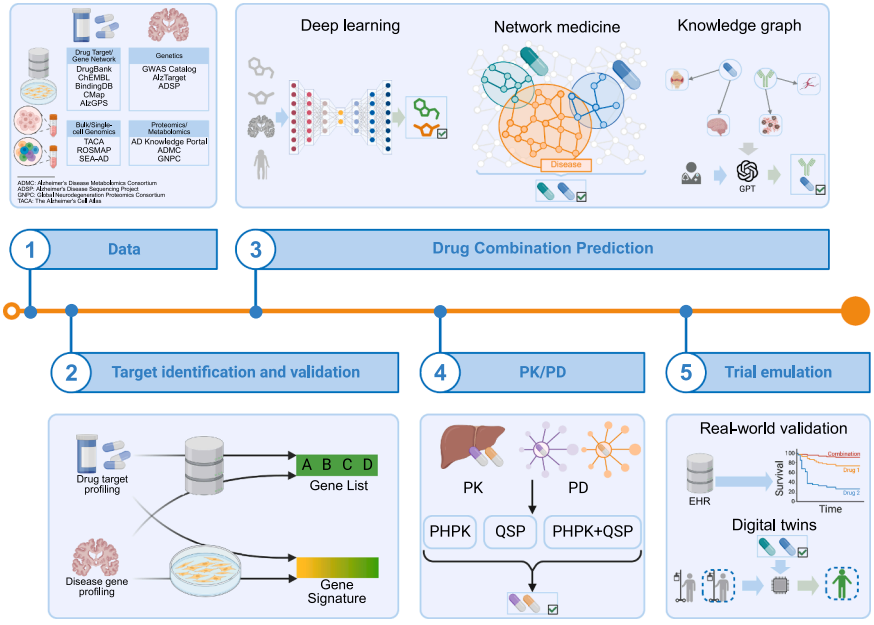

Fig. 1. A diagram illustrating computational framework for rational drug combination design in Alzheimer's disease. The entire process contain (1) high-quality data curation, (2) target identification and validation, (3) drug combination prediction using various computational approaches across deep learning, network medicine, knowledge graph approaches, and others; (4) Pharmacokinetics (PK) and Pharmacodynamics (PD) prediction and validation, and (5) Trial emulation to validate real-world efficacy of prioritized drug combinations from real-world patient data before future clinical trial testing. EHR: Electronic Health Record; QSP: Quantitative Systems Pharmacology; PHPK (PBPK): Physiologically based pharmacokinetic modelling.

Table 1
A list of drug combinations that have been tested in Alzheimer's disease clinical trials for therapeutic effect tested since 2015.

Combination	Therapeutic Purpose	CADRO	Clinical Trial	Phase	Overall Status
Pharmacodynamic combinations					
Albumin + Immunoglobulin	Disease-targeted therapy	Amyloid beta	NCT01561053	Phase 2/3	Completed
Baclofen + Acamprosate	Cognitive enhancer	Neurotransmitter Receptors	NCT02361242	Phase 2	Completed
Ciprofloxacin + Celecoxib	Disease-targeted therapy	Inflammation	NCT06185543	Phase 2	Recruiting
Cromoglicic acid + Ibuprofen	Disease-targeted therapy	Inflammation	NCT02547818	Phase 3	Completed
			NCT04570644	Phase 1	Completed
CST-2032 + CST-107	Cognitive enhancer	Neurotransmitter Receptors	NCT05104463	Phase 2	Completed
DAOIB + AO	Cognitive enhancer	Multi-target	NCT06467539	Phase 2	Recruiting
Dasatinib + Quercetin	Disease-targeted therapy	Inflammation	NCT04063124	Phase 1/2	Completed
			NCT04685590		Active, not recruiting
			NCT04785300	Phase 2	Enrolling by invitation
			NCT05422885	Phase 1/2	Completed
				Phase 1/2	
Donanemab + LY3202626	Disease-targeted therapy	Amyloid beta	NCT03367403	Phase 2	Completed
Donepezil + Mefloquine	Cognitive enhancer	Neurotransmitter Receptors	NCT03698695	Phase 1	Completed
Donepezil + Memantine	Cognitive enhancer	Synaptic Plasticity/ Neuroprotection	NCT03802162	Phase 1	Completed
			NCT04229927	Phase 3	Unknown status
Donepezil + Solifenacin	Cognitive enhancer	Neurotransmitter Receptors	NCT02185053	Phase 2	Completed
			NCT02434666	Phase 2	Completed
			NCT02549196	Phase 2	Completed
			NCT02860065	Phase 2	Withdrawn
Dronabinol + Palmitoylethanolamide	Neuropsychiatric symptom treatment	Neurotransmitter Receptors	NCT05239390	Phase 2	Unknown status
E2814 + Lecanemab	Disease-targeted therapy	Multi-target	NCT01760005	Phase 2/3	Recruiting
			NCT05269394		Active, not recruiting
			NCT06602258	Phase 2/3	Recruiting
				Phase 2	
Insulin + Empagliflozin	Disease-targeted therapy	Metabolism and Bioenergetics	NCT05081219	Phase 2	Completed
Losartan + Amlodipine	Disease-targeted therapy	Vasculature	NCT02913664	Phase 2/3	Completed
LY3202626 + Itraconazole	Disease-targeted therapy	Amyloid beta	NCT02323334	Phase 1	Completed
MK-1708 + Itraconazole	Not available	Not available	NCT06586606	Phase 1	Completed
Polypill	Cognitive enhancer	Not available	NCT06597058	Phase 2	Recruiting
Rotigotine + Rivastigmine	Cognitive enhancer	Neurotransmitter Receptors	NCT06702124	Phase 3	Recruiting
RQC	Disease-targeted therapy	Amyloid beta	NCT06470061	Phase 2	Not yet recruiting
Sabirnetug + rHuPH20	Disease-targeted therapy	Amyloid beta	NCT06511570	Phase 1	Completed
Simvastatin + *l*-Arginine + Sapropterin	Disease-targeted therapy	Synaptic Plasticity/ Neuroprotection	NCT01439555	Phase 2	Completed
Sodium oligomannate + Memantine	Disease-targeted therapy	Gut-Brain Axis	NCT05430867	Phase 4	Unknown status
STA-1 + Donepezil	Cognitive enhancer	Synaptic Plasticity/ Neuroprotection	NCT01255046	Phase 2	Unknown status
Tauroursodeoxycholic acid + Phenylbutyric acid	Disease-targeted therapy	Cell death	NCT03533257	Phase 2	Completed
Tdap vaccine	Disease-targeted therapy	Inflammation	NCT05183516	Phase 1/2	Unknown status
Wujia Yizhi	Disease-targeted therapy	Inflammation	NCT06534723	Phase 3	Recruiting
Pharmacokinetic combinations					
Dextromethorphan + Bupropion	Neuropsychiatric symptom treatment	Neurotransmitter Receptors	NCT03226522	Phase 2/3	Completed
			NCT04797715	Phase 3	Completed
			NCT04947553	Phase 3	Completed
			NCT05557409	Phase 3	Completed
			NCT06736509	Phase 3	Enrolling by invitation
Dextromethorphan + Quinidine	Neuropsychiatric symptom treatment	Neurotransmitter Receptors	NCT02442765	Phase 3	Completed
			NCT02442778	Phase 3	Completed
			NCT02446132	Phase 3	Terminated
			NCT02534038	Phase 2	Terminated
			NCT03393520	Phase 3	Completed
			NCT04408755	Phase 3	Terminated
			NCT04464564	Phase 3	Terminated
Side effect management					
Xanomeline + Trospium	Neuropsychiatric symptom treatment	Neurotransmitter Receptors	NCT05511363	Phase 3	Recruiting
			NCT05980949	Phase 3	Recruiting
			NCT06126224	Phase 3	Recruiting
			NCT06585787	Phase 3	Recruiting

identification and prioritization. Here, the candidate genes can also be cross-referenced with more genetic evidence from resources such as the Genome Center for Alzheimer's Disease (GCAD) and the Alzheimer's Disease Sequencing Project (ADSP) [13]. GCAD offers harmonized whole-genome sequencing (WGS) and whole-exome sequencing (WES) data, while ADSP (via NIAGADS) provides over 58,000 WGS and 19,000 WES datasets from 66 cohorts as of May 2025. Clinical and phenotypical data are available through resources such as the National Alzheimer's Coordinating Center (NACC) and the Alzheimer's Disease Neuroimaging Initiative (ADNI) [14]. NACC offers a Uniform Data Set (UDS) of over 54,000 participants, 200,000 clinical assessments, and 8300 neuropathology exams from 36 Alzheimer's Disease Research Centers (ADRCs). The ADNI dataset is composed of longitudinal clinical, imaging, genetic, and other biomarker data from 2500 participants from over 60 clinical sites in North America. General drug-target and chemical-biology databases (Fig. 1) can also be used to assess the druggability of candidate genes, such as ChEMBL [15], BindingDB [16], and DrugBank [17]. These resources contain experimentally measured bioactivity and binding affinity data. DrugBank, for example, has comprehensively profiled over 17,000 drugs (FDA-approved, investigational, experimental, withdrawn, etc.) as of 2025 [17].

Recently, network-based approaches for drug repurposing [18] and prediction of drug combinations [19] have challenged the traditional "one gene, one drug, one disease" paradigm for AD. To this end, AlzGPS [20] and The Alzheimer's Cell Atlas (TACA) [21] have been developed. These resources contain large-scale multi-omics data (genomics, transcriptomics, proteomics, and interactomics) and network- and gene-expression-based drug prioritization for over 3000 FDA approved/investigational drugs and 700,000 drug perturbation profiles [20,21]. TACA also offers an interactive explorer of 1.1 million fully annotated brain cells. To summarize, there is a growing multitude of resources that provide critical tools for AD drug development that can be applied through computational methods to advance drug combination research.

4. Endophenotype-based drug combinations

Endophenotypes represent intermediate pathobiological phenotypes that bridge genetic and disease phenotypes [22]. In AD, endophenotypes capture specific pathobiological processes such as amyloid deposition, tauopathy, neuroinflammation, metabolic dysfunction, and others [18,23]. Targeting these endophenotypes offers a promising avenue for drug combination design, as drugs that modulate the molecular pathways driving these endophenotypes may offer therapeutic benefits across diseases sharing common pathologies. Targeting disease at the level of endophenotypes rather than clinical symptoms potentially offers a more effective way to identify disease-modifying therapies [18,23]. However, given the multifactorial nature of AD, combination therapy (or "cocktail" therapy [24]) is often essential even when addressing endophenotypes. In addition, combining multiple drugs can improve treatment outcome through two avenues: multi-endophenotype targeting [25] and complementary endophenotype targeting [19].

As an example of multi-endophenotype targeting, Fang et al. proposed sildenafil for AD, using an endophenotype-based network medicine strategy that considered sildenafil's capabilities in targeting multiple amyloid and tau endophenotypes [18]. In addition, sodium oligomannate has shown efficacy in reducing Aβ aggregation and neuroinflammation while also improving gut microbiota [26]. Several existing AD drug combination therapies also reflect multi-endophenotype targeting principles. For example, Shang et al. recently demonstrated that a combination treatment targeted at AD risk-increasing diseases, including diabetes, dyslipidemia, hypertension, and inflammation, delays the onset of cognitive deterioration [27]. This revealed that the concurrent use of anti-diabetic medications, lipid-lowering drugs, antihypertensive medications, and non-steroidal anti-inflammatory drugs could target multiple pathologies of AD and significantly slow disease progression. Multitarget immunotherapy is also being studied, such as the combination of Aβ and pTau vaccines, which has been shown to reduce amyloid plaques, tau tangles, and neuroinflammation in AD rodent models [28]. Lastly, a recent trial combining the anti-amyloid antibody lecanemab with the anti-tau antibody E2814 is aiming to target amyloid and tau endophenotypes simultaneously (see Table 1).

To date, multi-target drugs for AD have been predominantly designed empirically. Here, we highlight an *in-silico* network medicine framework that provides a rational drug combination design via synergistically targeting multiple AD/ADRD endophenotypes (Fig. 2). This framework incorporates multi-modal data to establish endophenotype-based biological networks or pathways and drug target profiles for mechanistic interpretation (i.e., mechanisms-of-action) of combination effects based on the protein-protein interactome network [19]. Drug combinations are ranked by their ability to complementarily target different endophenotypes while avoiding adverse drug-drug interactions, as highlighted in a recent study which created an *in silico* network medicine-based approach to prioritize drug combinations [19].

For a network-based approach to AD drug combinations to be effective, however, it must be established whether or not the topological relationship between two drug-target modules reflects biological relationships underlying AD biological endophenotypes, while also quantifying their network-based relationship to AD-related biological network modules. A key assumption is that a drug combination is therapeutically effective only if it follows a specific relationship to the endophenotype module (such as synergistically targeting both amyloid and tau endophenotypes [18]), as captured by *Complementary Exposure* patterns [19] in the target modules of both drugs (Fig. 2C), without overlapping toxicity.

Fig. 3 further illustrates this multi-endophenotype targeting concept by generalizing the existing Complementary Exposure pattern described in Fig. 2C—originally defined on a single disease module—to the broader context of multiple AD-related pathologies. Fig. 3A presents three rational pharmacodynamics-based design patterns: (i) *Multi-target drugs*, in which a single agent affects multiple endophenotypes (e.g., amyloid and tau) by modulating shared core genes. However, this strategy may carry an elevated risk of toxicity, as these shared genes often participate in other essential biological processes unrelated to AD. Targeting such genes may lead to side effects, making this approach less suitable for elderly AD patients. In practice, many cancer drugs exhibit broad multi-endophenotype targeting, but the potential risks of these agents may outweigh their benefits in AD patients. (ii) *Multi-target combinations*, where two drugs independently target distinct disease modules to achieve broader pathological coverage while minimizing adverse effects. (iii) *Multi-target combinations with complementary exposure*, in which multiple drugs collectively target key AD endophenotypes through mechanistically distinct and non-overlapping pathways. This approach maximizes therapeutic breadth while minimizing redundancy and drug–drug interference. Fig. 3B provides real-world examples aligned with these design patterns: *sildenafil* exemplifies a single multi-target drug [18]; E2814 + Lecanemab and Donepezil + Memantine represent dual-drug combinations that achieve complementary targeting of amyloid and tau endophenotypes through distinct mechanisms. In contrast, Dextromethorphan + Bupropion (AXS-05) is highlighted as a pharmacokinetics-based combination that enhances therapeutic efficacy through metabolic interaction. Notably, such drug–drug interaction–dependent combinations fall outside the scope of the pharmacodynamics-focused design patterns in Fig. 2A, which are defined in the principle of minimizing direct interactions between drug modules to preserve mechanistic independence.

5. Drug combinations for co-pathologies/proteinopathies in ad/adrd

AD/ADRD are characterized by the hallmark pathologies of amyloid

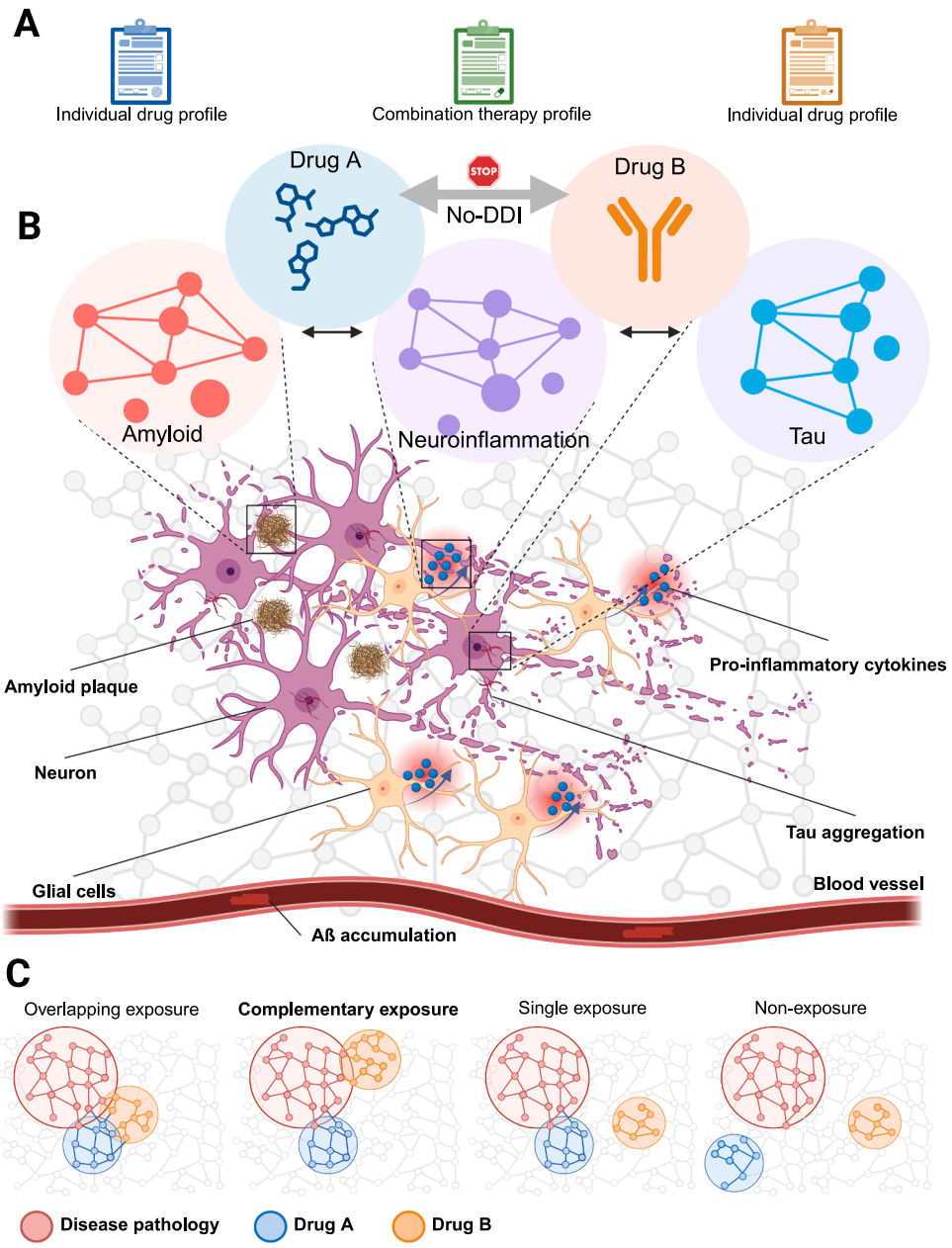

Fig. 2. Conceptual framework of rational drug combination design based on endophenotypes in Alzheimer's disease (AD). (A) Combinations of drugs are prioritized with joint consideration of a drug's disease relevance profile as well as its drug–drug interaction profile. Ideal combinations seek complementary coverage of disease mechanisms with minimal adverse interactions. **(B)** Disease relevance is characterized at the level of endophenotypes of AD (such as amyloid pathology, neuroinflammation, tauopathy) reflecting central mechanisms of disease progression. Therapeutic goal is slowing disease progression through intervention on these intermediate pathologies. **(C)** Four drug–disease interaction patterns are defined by the network proximity between a disease module and the network modules of two drugs. Overlapping exposure occurs when both drug modules overlap with the disease module and with each other; complementary exposure arises when both modules overlap with the disease module but remain distinct from one another; single exposure refers to only one drug module overlapping with the disease module; and non-exposure refers to neither drug module overlapping with the disease module.

plaques and neurofibrillary tau tangles, and also by the co-occurrence of additional proteinopathies, such as TDP-43 and α-synuclein [29]. These proteinopathies are especially prominent in cerebral amyloid angiopathy (CAA) [30], limbic-predominant age-related TDP-43 encephalopathy (LATE-NC) [31], and Lewy body disease (LBD) pathology [32]. Importantly, these neuropathological proteins exhibit cross-seeding phenomena at the cellular level, which creates synergistic pathological effects that cannot be addressed by targeting a single pathway or network. Additionally, patients with co-pathologies experience faster cognitive decline and show limited response to standard AD therapies that target a single proteinopathy alone. Therefore, drug combinations are necessary to simultaneously mitigate multiple proteinopathy pathways, blocking their cross-seeding interactions to provide comprehensive therapeutic coverage of mixed proteinopathies in AD/ADRD (Fig. 3A).

Another opportunity resides in the observation that vascular amyloid deposition occurs in 90 % of AD patients [30,33], disrupting blood-brain barrier (BBB) integrity and impairing perivascular clearance pathways that are critical for removal of amyloid and other waste from the brain. The co-occurrence of brain amyloid with CAA creates a unique cellular environment in vascular smooth muscle cells, pericytes, and neurons that is synergistically harmed by amyloid accumulation. Anti-amyloid

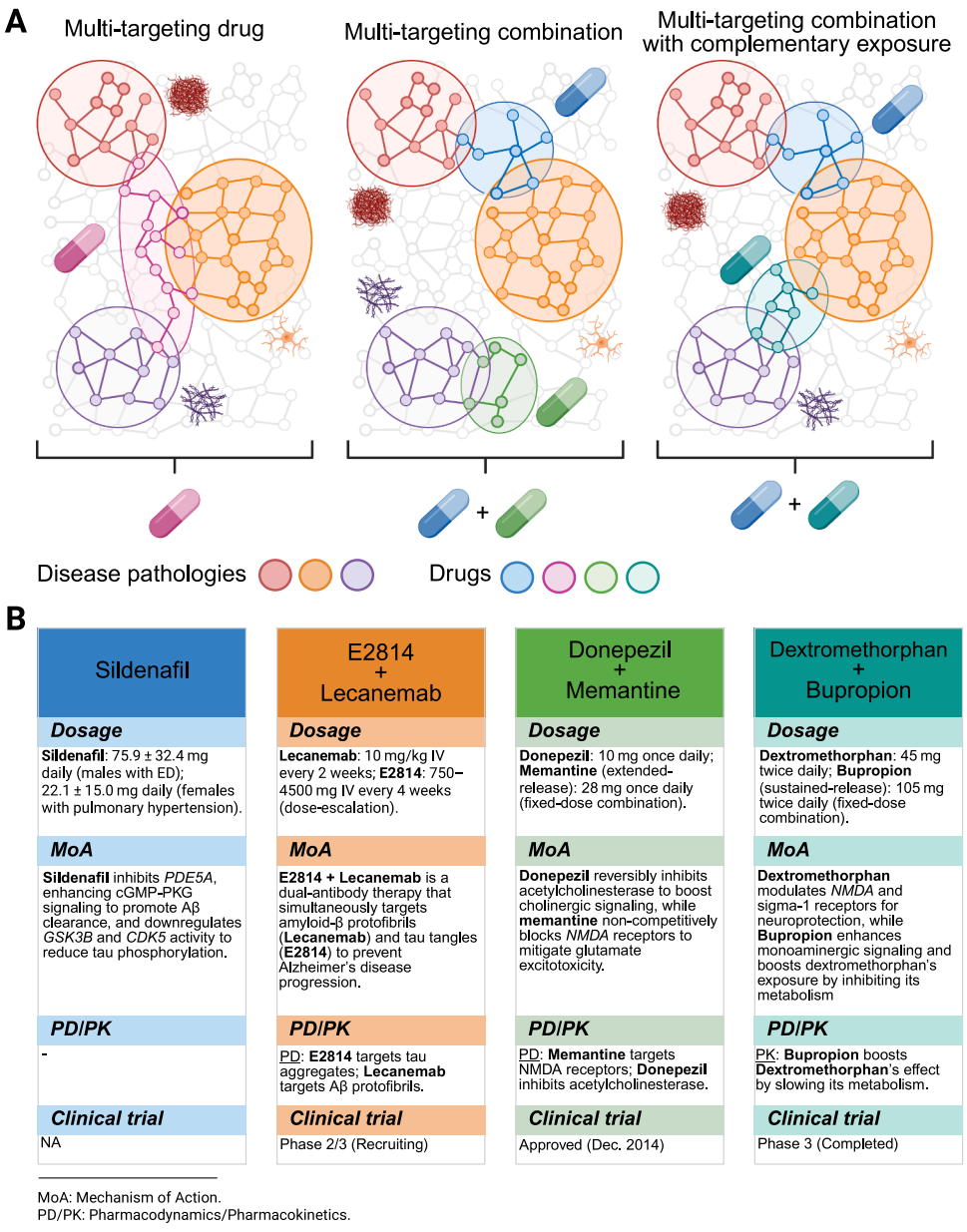

Fig. 3. Illustrative drug combination design patterns and real examples. (A) Conceptual framework of pharmacodynamics-based drug combination strategies targeting Alzheimer's disease (AD) pathologies. Three design patterns are illustrated: (i) *multi-targeting drugs* that affect multiple disease pathologies via single agents (e.g., by acting on shared core nodes); (ii) *multi-targeting combinations* using two drugs with distinct but complementary pathology targets to reduce adverse effects while broadening therapeutic coverage; and (iii) *multi-targeting combinations with complementary exposure*, where the most critical disease modules (e.g., neuroinflammation) are targeted through different molecular axes by multiple drugs. (B) Real-world examples that exemplify the design patterns. Sildenafil represents a single multi-pathology drug acting on amyloid and tau modules. E2814 + Lecanemab and Donepezil + Memantine illustrate dual-drug combinations that achieve broad pathology coverage via complementary mechanisms. Dextromethorphan + Bupropion represents a pharmacokinetics-based combination, in which Bupropion enhances Dextromethorphan's exposure, distinct from the pharmacodynamics-focused strategies depicted in Panel A.

immunotherapies, which target both brain and vascular amyloid deposits, can induce amyloid-related imaging abnormalities (ARIA) [3,34,35], an inflammatory response causing brain swelling or bleeding that is mechanistically similar to spontaneous CAA-related inflammation (CAA-ri) [36]. The PROGRESS trial [37] showed that lowering blood pressure reduced CAA-related brain hemorrhage by 77 %. These results suggests that combination trials using anti-inflammatory drugs and antihypertensive medications together with anti-amyloid immunotherapies may offer a better approach to manage ARIA while treating AD patients by simultaneously clearing amyloid deposits, controlling immune-mediated inflammation, and preventing bleeding complications.

Within neurons, LATE-NC involves the cytoplasmic and nuclear aggregation of TDP-43, affecting around 57 % of AD patients [38]. Recent studies [39,40] report that tau accumulation promotes TDP-43 mis--localization and aggregation, which in turn accelerates neurodegeneration. The synergistic relationships among different proteinopathies provides a rationale for combination therapy [39] that could disrupt the cycle of pathology by targeting multiple co-occurring disease cascades. Antisense oligonucleotides (ASOs) [41] are promising therapies for targeting TDP-43 in early stages of pathological development. Recent clinical advances include ethylene nucleic acid (ENA)-modified ASOs that reduce TDP-43 levels in mouse brain and spinal cord. These ENA-modified ASOs also show long-lasting behavioral

improvements by suppressing cytoplasmic TDP-43 aggregation. Notably, ASOs utilize oligonucleotide-based gene silencing [42] rather than protein binding and clearance, offering a therapeutic mechanism complementary to monoclonal antibodies. This mechanistic distinction may reduce potential drug interactions and allow for safer combination strategies.

Approximately 30 %−50 % of AD patients are positive for α-synuclein based on seed amplification assays (αS-SAAs) [43,44]. α-synuclein's C-terminal region binds to the tau microtubule-binding domain, while both proteins can cross-seed each other's aggregation [45,46]. This shared cellular dysfunction [29] induces mitochondrial impairment, synaptic dysregulation [47], and neuroinflammation [48]. Prasinezumab (Roche) [49], which targets the C-terminal region of α-synuclein, missed the primary outcomes but showed slower progression in loss of motor function in a specified subgroup, while cinpanemab [50] targeting the N-terminal region failed to meet primary endpoints. Targeting multiple proteins simultaneously could provide more comprehensive neuroprotection than single-target approaches (Fig. 3).

Mechanistically, combination approaches could also target distinct aspects of neuropathology: (1) anti-amyloid therapies address upstream amyloid triggers; (2) anti-tau immunotherapies and ASOs (BIIB080 from Biogen) target neurofibrillary pathology; (3) α-synuclein immunotherapies prevent protein spread and aggregation; (4) TDP-43 ASOs reduce RNA processing dysfunction; and (5) anti-inflammatory medications have been identified from the AD drug development pipeline [6] and existing drug repurposing studies [51]. The temporal and spatial

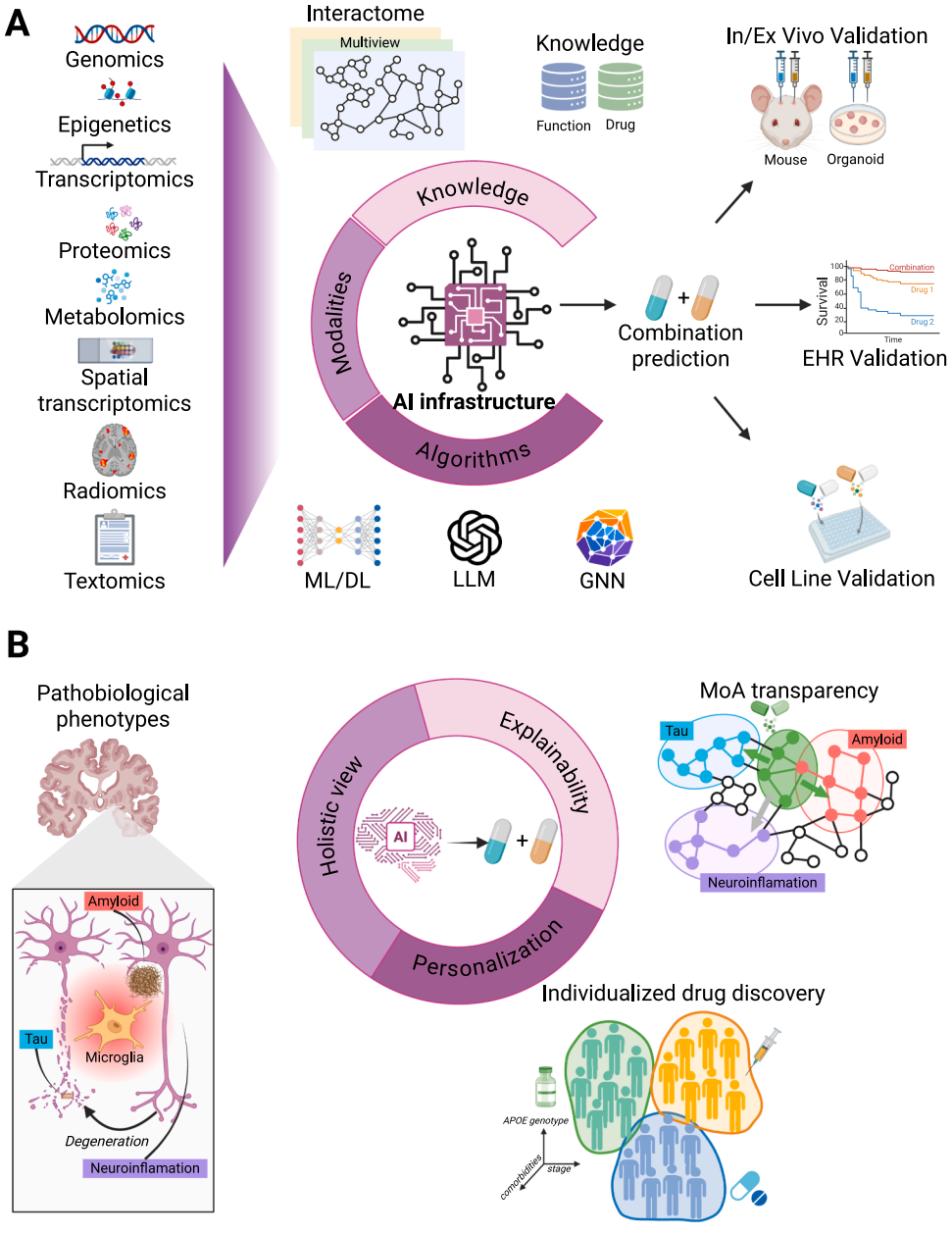

Fig. 4. Prospect for a next-generation framework for drug combination design centered on Artificial Intelligence (AI) and preclinical and clinical validation for Alzheimer's disease (AD). (A) A conceptual AI framework for AD drug combination discovery, leveraging multi-modal data (e.g. omics, clinical, imaging) and known biological information, and combing with experimental assays (including in vitro and in vivo models). Possible AI methods are graph neural networks, large language models, and deep learning methods. Drug discovery may also involve subsequent experimental verification. **(B)** Major functionalities of the system: (1) Holistic—capturing the multidimensional, interconnected aspects of AD pathobiology; (2) Explainability—giving interpretable explanations for drug combinations, which is essential for subsequent clinical trial verification pipeline; (3) Precision Medicine — addressing heterogeneity of disease progression to adapt personalized drug combination predictions to subphenotypes in the tissue-specific and cell type-specific manners.

distribution of these co-neuropathological changes suggests that early intervention with combination therapies might prevent the cascades of multi-protein aggregation, which is a major characteristic of late-onset AD/ADRD. However, combination drug trials also face challenges due to the complexity of managing multiple therapeutic agents, potential adverse drug interactions, and a lack of well-characterized, clinically actionable biomarkers and clinical primary/secondary endpoints. This will require careful clinical trial design and biomarker-guided patient selection in future clinical trials.

6. Applications of computational drug combination in AD

Identifying effective drug combinations for Alzheimer's disease (AD) requires navigating the intricate biological landscape of a highly heterogeneous and multifactorial disorder. The central challenge lies in the need to integrate complex, multimodal data while preserving biological interpretability. As illustrated in Fig. 4A, a conceptual AI framework for AD drug combination design may leverage diverse data modalities, ranging from multi-omics to radiomics and EHR data. In addition, to ensure the AI framework makes biologically meaningful predictions, we expect it to integrate biological knowledge, including but not limited to drug perturbation profiles, biological functions, and how genes interact with each other in PPI. Traditional approaches for drug combination design often lack the ability to incorporate multimodal biological data, while emerging deep learning methods, especially graph neural networks (GNNs) and large language models (LLMs), may serve as the computational backbone of this framework.

As shown in Fig. 4B, the next-generation AI infrastructure for drug combination discovery should embody three essential features: (1) holistic modeling that captures the multidimensional, interconnected aspects of AD pathobiology; (2) explainability of predictions to ensure mechanism-of-action transparency and facilitate subsequent clinical trial design; and (3) personalization to account for individual variability and subphenotypes, such as APOE genotype, disease stage, and comorbidities. These features require the adopted AI agent to navigate the multifactorial disease landscape in a biologically meaningful way. In the

Table 2
Comparative Analysis of Computational Drug Combination Discovery Approaches across different categories.

Model Class	Key Features	Advantages	Limitations
Traditional Machine Learning	Depends on pre-defined feature representations of disease and drugs (e.g. chemical fingerprints, targets, MoA profiles). Applies classical machine learning algorithms (e.g. Random Forest) to classify or regress combination impacts.	Interpretable prediction and computationally effective. Typically produces high precision (few false positives) for predicting synergistic pairs – e.g., Random Forest predictors obtained highest precision by multi-team study.	Limited in capturing complex non-linear or multi-modal patterns. May miss many true synergies (lower "hit rate"), for instance deep graph models may find more synergistic hits than simpler models (highlighting lower recall for Random Forest). Requires manual feature engineering, which can be labor-intensive and might not scale to rich multi-omics data.
Deep Learning	Employs multi-layer neural networks to automatically learn features from large-scale data (e.g. using drug chemical structures and gene expression profiles as inputs). Capable of combining multiple data types (for example, transformer can fuse chemical and transcriptomic modalities).	Captures high-dimensional, non-linear drug relationships and interactions without human feature design. Can combine multiple data modalities (chemical, genomic, phenotypic) and often achieves higher prediction. Certain models additionally apply biological knowledge for interpretability (e.g. TranSynergy incorporates drug-target network and PPI for pathway-level understanding).	Typically need huge training data and prone to overfitting with small data sets. The model is often a "black box" and not highly interpretable without specific explanation methods. Training is computationally costly and for many fields of AD often small datasets may significantly limit performance.
Network Medicine	Exploits biomedical interaction networks (PPI) to find disease "modules" and drug targets within the interactome. Uses network measures such as network proximity to estimate distance between drug targets and disease genes, and patterns such as complementary exposure to estimate multi-drug coverage of a disease module. Often uses multi-omics data to build context-specific AD pathology networks [1].	Biologically interpretable framework – predictions can be rationalized by network topology and known pathways. Particularly effective when drugs hit distinct parts of a disease network: following the complementary exposure principle (two drugs overlap the disease module but not each other). Thus, network models naturally prioritize mechanistically synergistic combinations. They can also incorporate diverse data (omics, pathways), grounding predictions in disease biology [2].	PPI could be biased and incomplete. Network based interpretation is often less-intuitive to non-experts in network biology than traditional approach. Additionally, traditional network proximity methods can not consider cell-type or patient-specific data, making this approach difficult to capture context-dependent effects.
Knowledge Graph	Constructs a large knowledge graph of heterogeneous biomedical entities (genes, proteins, drugs, diseases, etc.) and their relationships. Graph neural networks (GNNs) learn embeddings over this multi-relational graph, capturing interactions between entities in the graph (e.g. a drug–gene–disease path). Advanced models (e.g. TxGNN) may include an explainer module to promote prediction interpretation.	Integration of conflicting biomedical knowledge into one model that can make zero-shot predictions on new conditions. The path-based explanation can reveal the chain of biological relationships that led to drug–disease prediction, which can be utilized to find drug combinations with complementary functional impact.	Strongly dependent upon the accuracy and completeness of aggregated knowledge. Though they can give prediction explanations, interpreting and verifying those explanations still require the careful consideration of domain experts.
Quantitative Systems Pharmacology	Uses mechanistic mathematical models (differential equations) to simulate drug pharmacokinetics and pharmacodynamics.	Provides mechanistic insight for Hypothetical testing and can optimize dosing schedules and combination strategies in silico. Enables virtual trial design to predict efficacy and safety before clinical testing, supporting regulatory decisions.	Development is time- and knowledge-intensive, requiring extensive literature curation and expert knowledge. Models have high parameter dimensionality with uncertainty and require careful validation against clinical data.
Real-World Data & Digital Twins	Uses real-world patient data to create virtual patient models and simulate clinical trials in silico. Performs trial emulation and statistics to simulate randomized controlled trials with observational data.	Enables high-throughput, cost-effective exploration of drug combinations using existing patient data. Allows optimization of trial design by testing different parameters virtually before conducting actual trials, supporting precision medicine through individualized treatment predictions.	Confounding and bias are major concerns since real-world patients aren't randomized. After careful co-founding adjustment, there may still be unmeasured confounders.

following sections, we review recent advances in machine learning, deep learning, network- and knowledge graph-based methods, and quantitative systems pharmacology models, providing an overall assessment of our current state and the existing gaps we have in realizing the desired AI agent for drug combination design in AD. Key features, advantages, and limitations of each major type of computational approaches are illustrated in Table 2.

6.1. Machine learning and deep learning

Conventional machine learning (ML) algorithms can meaningfully aid in drug combination discovery when effective feature engineering is undertaken to represent relevant biological features. For instance, El-Hafeez et al. [52] showed that random forest (RF) and ridge regression models effectively classify synergistic combinations and predict sensitivity scores using the metrics of drug mechanisms-of-action (MoA) and chemical similarity. Likewise, Pourmousa et al. [53] found that RF and XGBoost enhanced predictive precision, while graph convolutional networks (GCNs) improved hit rates at the cost of increased false positives for drug combination prioritization. These classic ML models rely on engineered features, such as molecular fingerprints or averaged MoA vectors, to represent drug combinations, balancing interpretability with predictive power. However, their reliance on pre-defined features limits scalability to multi-modal AD data, which frequently requires the integration of proteomic, transcriptomic, and clinical endpoints.

Deep learning (DL) models, such as DeepSynergy [54] and MatchMaker [55], incorporate data-driven feature extraction pipelines based on drug chemical fingerprint and gene expression profiles to predict drug combinations. Transfer-learning models extend this ability by enabling patient-specific predictions of synergy from patient-derived data in ways that facilitate personalized combination therapy [56]. Further advanced models, such as DeepSynBa [57] and TranSynergy [58,59], increase the biological relevance of the prediction. DeepSynBa identifies dose-response profiles from predictions on parameters of the Hill function and possesses a more informative output of a pharmacological choice [57], while TranSynergy includes biologically-informed drug-target profiles diffused through protein-protein interaction networks and provides novel mechanistic insight through pathway-level interpretability [58,59].

Transformer models have also recently become proficient tools for dealing with multi-modal fusion for the prediction of drug combinations. A recent study demonstrated the combined use of unsupervised machine learning (including vector representations of molecular structures and fingerprints) and experimental validation of new mitophagy-inducing compounds (Kaempferol and Rhapontigenin) for potential prevention of AD [60]. MADRIGAL [61] showcases this trend through BERT-mediated encoding of chemical forms and their fusion with gene expression and pathway-level information employing attentional mechanisms. MADRIGAL [61], in turn, combines transcriptomic, structural, and viability features and reveals an advanced level of multimodal synthesis already potentially transferable to neurodegenerative disease settings such as AD. These models show the evolution from static, feature-based learning towards dynamic, context-sensitive representations that capture complex drug-disease mechanisms.

6.2. In silico network medicine approaches

Network-based drug combination prediction is an alternative method of drug combination design for complex diseases like AD. Specifically, network-based methods utilize the topological and functional organization of molecular interaction networks to perform more biologically relevant drug combination predictions compared to traditional ML/DL methods [19]. Importantly, graph-based machine learning algorithms, e.g. GNN, represent a data-driven, network-based framework for drug combination design, as they integrate molecular interaction networks with multi-omics data to learn biologically meaningful representations. This enables more accurate and biologically grounded drug combination predictions.

The cornerstone of state-of-the-art network-based drug combination prediction is network proximity, which measures the topological similarity between drug targets and disease-relevant genes within the human protein-protein interactome [22,19,62]. Network proximity quantifies the likelihood that a drug will modulate a disease module in a specific disease network. Within network medicine [63], network proximity identifies "network drugs" that do not directly overlap with the disease module but exhibit relatedness within the protein-protein interaction network [64].

A previous study [19] generalized the application of network proximity to predict drug combinations, justifying that the most effective drug combination may involve drugs exposed to disease modules complementarily (Fig. 1C). Conceptualized upon network proximity, complementary exposure refers to two drugs that are found to significantly modulate a disease module while being separate from one another. Based on these theoretic principles in network proximity, a genome-wide positioning framework (termed AlzGPS) was developed for AD target discovery and drug repositioning [20]. AlzGPS also enables larger context support for combination design through MoA network visualizations and multi-endophenotype profiling. Together, this line of effort indicates that integrating protein-protein interaction networks into drug combination prediction improves interpretability and prioritization efficiency, with potential for identifying more effective treatments for AD/ADRD.

Performance of the network proximity-based approach can be improved when combined with multi-omics data, which facilitates the construction of disease and drug modules within patients' multi-omics profiles such as transcriptomics, proteomics and drug perturbation responses, rather than solely from literature or existing databases. Iida et al. exemplify this approach through SyndrumNet [65], which integrates PPI, transcriptome, diseasome, and drug-response profiles to predict synergistic drug combinations. SyndrumNet leverages both network proximity and transcriptional similarity between drug and disease modules to generate synergy scores. Further in vitro validation shows that 14 out of 17 top-predicted pairs demonstrated synergistic effects, confirming the biological relevance and translational potential of this integrated approach [65]. Similarly, Li et al. [66] employed transcriptomic data to define disease and drug-gene signatures. The orthogonality between these gene signatures is used together with network proximity to predict potential synergistic drug pairs [65]. Thus, integrating multi-omics data enables drug and disease modules to proceed with more grounding in biology, enhancing the disease specificity of network proximity prediction.

Notably, the availability of graph-based deep learning models [67,68] has enabled network-based drug combination discovery to consider network data and multi-omics data simultaneously, enabling data-driven drug combination prioritization with high accuracy. These models not only automate feature extraction from large, multi-modal data but also enable the construction of biologically meaningful representations (or embeddings) of genes, drugs, and cell contexts when applied to the PPI network. These embeddings reflect the functional roles and interconnectivity of genes more effectively than raw omics profiles alone. NETTAG, for example, is a graph-based method that learns gene embedding from PPI based on GNN [69]. By integrating human brain specific omics data, NETTAG identified 156 CE-associated genes for subsequent drug prediction. Similarly, Morselli Gysi et al. employed a consensus framework (CRank) that aggregates AI-based embeddings, diffusion-based similarity, and network proximity to drug prioritization [64]. For drug combination prediction, MGAE-DC [70] and PRODeepSyn [71] incorporate PPI into multi-modal frameworks that also integrate multi-omics data. MGAE-DC [70] employs a multi-channel graph autoencoder to distinguish between synergistic, additive, and antagonistic combinations, while PRODeepSyn uses a graph convolutional network [72] to embed cell lines by combining

explicit omics features with latent network-derived embeddings. These approaches are commonly validated using benchmark datasets [73], which have been used to evaluate drug synergy across 22,737 experiments covering multiple cell lines. Notably, such benchmarks reveal that synergy is highly context-dependent, underscoring the need for drug prediction that captures both global network structure of genes and local cell-type-specific context. In this regard, the multi-modal capability of graph-based machine learning algorithms is essential.

6.3. Biomedical knowledge graph

The use of biomedical knowledge graphs (KGs) offers additional advances beyond network-based methods in disentangling complex biological interactions for predicting combination medicines for AD. In contrast to PPI networks, KGs provide a more comprehensive framework for integrating multimodal biomedical data and heterogeneous network node types and their interplay relations. This allows KG to integrate sophisticated drug-disease interactions in greater detail.

The explanatory power of KGs for drug discovery benefits greatly from its advancement in representation and reasoning methods. Similar to the network based machine learning method for PPI, the embeddings of nodes (i.e., drugs or targets/proteins) in KG additionally captures their semantic and structural information, allowing subsequent prediction tasks, such as prediction of therapy for AD. Models like GNN in TxGNN [74], Relational Graph Convolutional Networks (R-GCNs) in PlaNet [75], and Knowledge Graph Convolutional Networks (KGCN) in KGCN—NFM [76], propagate information along graph nodes, capturing higher-order dependencies. For example, Su et al. created a comprehensive KG called the integrative Biomedical Knowledge Hub (iBKH) by harmonizing and integrating information from diverse biomedical resources for AD drug repurposing [77].

Explainability is another major strength of the KG-based approach, especially for clinical translation tasks. Methods such as multi-hop path-based explanation, as used in the TxGNN Explainer, give intelligible rationales for predictions through tracking biological pathways and interactions supporting the effectiveness of a drug. Similarly, PlaNet [75] provides influence scoring for the detection of population characteristics influencing treatment safety, while KGCN—NFM checks its predictions through pathway and interaction analysis, ensuring biological feasibility.

The use of KGs in drug discovery pervades multiple critical areas, especially the treatment challenges of AD. One strength is their capacity for zero-shot and few-shot predictions, facilitating the detection of therapeutic candidates for new-onset diseases or rare combinations of drugs. TxGNN, for example, relies on knowledge transfer between mechanistically similar disease conditions for predicting treatment for conditions with no known therapy [74]. The concept of endophenotypes as shared biological modules of complex disease [22] can also be applied, as distinct diseases may share similarity at the endophenotype level, making them well-suited for one-shot or few-shot prediction tasks based on existing KG models. PlaNet further showcases the same through predicting the effectiveness and safety for new drugs and new combinations based on structural and semantic generalization [75]. In addition, KGs are skilled in modeling the interactions and synergy among drugs. For example, the KGCN—NFM approach, through the coupling of drug structures with an extensive knowledge graph, detects synergistic drug pairings through examining their activities on disparate nodes in biological pathways.

6.4. Quantitative systems pharmacology (QSP) model

Another challenge in the rational design of drug combinations is to accurately predict pharmacokinetic properties and dosing regimens. Physiologically based pharmacokinetic (PBPK) models can simulate the relationship between drug dosage, route of administration, and drug concentration in different human biological systems. Chang et al., for example, developed a PBPK model to characterize brain disposition of anti-amyloid antibodies [78]. This PBPK model included a brain compartment including cerebrospinal fluid (CSF) circulation system and brain parenchyma, as well as 15 other tissue compartments, each including plasma, blood cell, endosomal, interstitial, and cellular sub-compartments. The compartments were assumed to connect to each other via blood and lymph flow, and antibodies were assumed to travel from plasma to interstitial fluid, and to enter the brain via bulk flow through the blood–brain barrier (BBB) and the blood-CSF-barrier (BCSFB). The model was developed from published parameters and preclinical animal experiments and translated to humans by changing the values of the corresponding physiological parameters. Notably, this model could predict the brain disposition for two antibody combination by using the corresponding PK parameters.

The QSP model can also simulate the effect of drug on biomarkers and disease modeling in AD/ADRD [79], aiming to represent the complex relationship between pharmacokinetics (PK), biological systems, molecular pathways, biomarkers, and clinical outcomes. Thus, QSP models often involve a system of differential and algebraic equations, and a large amount of model parameters. For an established QSP model, different drugs may have different drug-related parameters, such as binding affinity and drug-mediated clearance rate of Aβ, while all drugs can share the same non-drug-related parameters, such as natural rates of Aβ production, clearance, and aggregation.

Although QSP models primarily evaluate individual drugs, they can also be used to predict the effect of drug combinations with the corresponding drug-related parameters. For instance, as aducanumab binds to Aβ oligomers/plaques and solanezumab binds to Aβ monomers, a computational model could assume the aducanumab-solanezumab combination binds to all of Aβ monomers, oligomers, and plaques. In this case, the computational model could use the corresponding parameters to simulate the effect of the drug combination on all Aβ monomers, oligomers, and plaques. As another example, Madrasi et al. integrated a QSP model to simulate the longitudinal relationship between drug exposure and Aβ [80], focusing on the production, transport, and aggregation of Aβ in circulation plasma, peripheral tissue, brain interstitial fluid, and CSF. The model was calibrated with respect to PK parameters for anti-Aβ antibodies (aducanumab, crenezumab, solanezumab, bapineuzumab), beta secretase inhibitors (elenbecestat and verubecestat), and the gamma secretase inhibitor semagacestat, while also incorporating drug-specific binding affinity and clearance rates of Aβ (monomer, oligomer and plaque) for aducanumab, crenezumab, solanezumab, bapineuzumab, and binding properties of beta/gamma secretase for elenbecestat, verubecestat and semagacestat. This model was shown to predict the effect of a two-antibody combination by using the corresponding PK parameters, binding affinity, and clearance rates of Aβ, or the effect of an antibody and inhibitor combination by using the drug-specific parameters related to PK, Aβ, and beta/gamma secretase.

Mazer et al. also developed a quantitative semi-mechanistic model for amyloid, tau, and neurodegeneration in AD known as the Q-ATN model [81]. This model characterized the longitudinal relationship between drug-mediated changes in Aβ plaque, Aβ plaque-modulated tau production, tau-modulated cortical thinning, and cortical thickness-associated Clinical Dementia Rating - Sum of Boxes (CDR-SB). The model was calibrated for anti-Aβ antibodies, including aducanumab, gantenerumab, lecanemab, bapineuzumab, and donanemab. Notably, this predicted the effect of a two-antibody combination on CDR-SB by using the corresponding parameters of drug-mediated changes in Aβ plaque.

The PBPK model and QSP model can be integrated as well, as exemplified by Geerts et al., to predict Aβ PET imaging and amyloid-related imaging abnormalities with edema (ARIA-E) outcomes [82, 83]. The compartments in the PBPK model included peripheral tissue, lymph, plasma, four different CSF compartments, interstitial fluid (ISF), and BBB, while the components of the QSP model characterized the biological pathways of Aβ aggregation, microglia-mediated and

antibody-mediated Aβ clearance, and *APOE* genotype. Additionally, the QSP component characterized the relationship between CSF Aβ and standardized uptake value ratio (SUVR), as well as amyloid aggregation in the perivascular compartment, macrophage activity, and ARIA-E. The model was calibrated for anti-Aβ antibodies, including aducanumab, crenezumab, gantenerumab, lecanemab, and solanezumab. This model could predict the PET-scan and ARIA-E outcomes for a pairwise anti-Aβ antibody combination by using the corresponding parameters of PK and Aβ binding infinity.

Geerts et al. also employed this strategy of integrating PBPK and QSP models to predict outcomes for anti-tau and anti-synuclein antibodies (tilavonemab, prasineuzumab, gosuranemab, prasineuzumab and semorinemab) [84]. The PBPK component was similar to previous work [82,83], while the QSP model characterized tau and α-synuclein secretion, antibody binding, and internalization inside the postsynaptic neuronal compartment. In theory, this model could be integrated with other models to predict the effect of combinations involving anti--Aβ/tau/α-synuclein antibodies. However, it is still challenging to conduct additional model calibration because of complex PK profiles involved in different types of drug combinations, including small molecule / antibody combinations.

6.5. Real world data-derived drug combination

Integrating real-world data (RWD) from diverse sources (e.g., electronic health records [EHRs] and health insurance claims) that reflect real-world patients treated in clinical settings, combined with high-quality research cohort data enriched with biomarkers, genetics, and imaging, is pivotal for advancing the discovery of effective AD/ADRD drug combinations. Thus, the growing RWD, biomarker, genetics, multi-omics, and clinical trial data have the potential to allow increasingly individualized predictions of drug combination trial outcomes based on complex relationships between baseline features, trajectories of decline, drug mechanisms, and clinical and biomarker characteristics across disease progression of AD/ADRD.

Recently, an emerging technology (digital twins) has allowed us to go beyond simple simulation to create a fully reconstructed virtual ecosystem *in silico*. By combining machine learning and statistical methods within the *in silico* digital twins environment, the impact of perturbing the virtual ecosystem on RWD can be modelled rapidly [85], including APOE genotypes, sex, and other related information. Digital twins offer efficient information for trial design because multiple trial parameters can be manipulated and the joint influence on trial performance can be readily estimated in the design stage of the drug combination trials. Researchers can develop multimodal machine learning models to estimate the treatment effect of each drug combination from real-world patient data, PubMed publications of relationships connecting drugs, diseases, genes, anatomies, pharmacologic classes, and side effects, and existing biomarkers and AD/ADRD cohort studies. Researchers could consider the following two setups: (1) investigating whether the drug can prevent cognitive normal control (NC) patients from being diagnosed with AD/ADRD; and (2) investigating whether the drug can prevent patients with mild cognitive impairment (MCI), or various endophenotypes derived from tau, amyloid PET, and plasma and CSF biomarkers, from progressing as rapidly to AD. A drug combination's efficacy can be defined by (1) a reduced rate of AD onset or clinical score, or (2) a slower progression to AD from at-risk non-AD (i.e. 65 years older) or MCI patients. In order to evaluate the differential treatment effectiveness on patients with different progression rates (duration between healthy controls to AD, or MCI to AD), the matched controls can be stratified into different sub-phenotypes and then run through a trial emulation pipeline to estimate the efficacy of combination treatments between the treatment group and each control group [86]. One major challenge of RWD-supported drug combination outcome analysis is confounding justification. Beyond traditional propensity score-matching analysis [18,87], target trial emulation [88] may reveal more accurate causal relationships between AD/ADRD outcomes with a specific drug combination.

6.6. Toward an ideal AI agent for drug combination design in AD

An ideal AI agent for drug combination design in AD should achieve holistic modeling, explainability, and personalization (Fig. 4B). Overall, holistic modeling is supported by recent methods that incorporate multi-omics data to better understand both disease processes and drug effects. Network-based approaches, particularly KG, provide a unified framework to integrate insights from diverse data types (such as APOE genotypes, transcriptomics and proteomics profiles of individuals) and biological knowledge, supporting a systems-level understanding of AD. For explainability, most deep learning and graph-based models remain black boxes; however, TxGNN-Explainer [74] offers a promising step forward by tracing multi-hop biological paths that justify model predictions. Personalization remains the most underdeveloped aspect; current AI algorithms for drug combination design often rely on population-level insights and fail to capture individual heterogeneity in the tissue or cell type-specific context. For instance, an AI agent assembles digital twins may predict disease progression, discovering biomarkers, identifying new drug targets and opportunities for drug development, facilitating clinical trials, and advancing precision medicine for AD/ADRD [85].

7. Experimental validation of drug combinations

Several experimental models can be used to evaluate preclinical evidence of efficacy, synergy, toxicity, target engagement, mechanism-of-action, route of administration, dose range, schedule of administration for drug combination, such as mouse models or human cell-based model systems. Human induced pluripotent stem cells (iPSC), which capture identical risk alleles as the donor individuals, offers a new approach for deciphering disease mechanisms with higher predictability of their effects in humans[89–93], and identifying disease-relevant drug mechanisms with respect to both clinical efficacy and side effects [90,94,95]. For example, patient iPSC-derived neurons and microglial models have been applied to test drug mechanisms-of-action [18,51,96]. Beyond cell-based in vitro models, patient iPSC-derived brain organoids or vascularized neuroimmune organoids may offer better model systems to test drug effects, such as lecanemab [97]. However, there are several challenges to test AD drug combinations using these in vitro, *ex vivo*, or in vivo models. For example, there is still no well-established combination therapy index to quantify the synergy of drug combinations in these experimental models. Beyond traditional phenotypic assays in cell models or cognitive behavior testing in animal models, multi-omics (including transcriptomics and proteomics) may offer new approaches to test and establish evidence of efficacy, synergy, toxicity, and target engagement for candidate drug combinations[98].

7.1. Challenges in regulatory science and trial innovation for AD drug combinations

There is an urgent need to optimize trials, terminate trials of agents at the earliest point where success becomes unlikely, and support those drug combinations that have a high likelihood of becoming important new therapies. Existing data, including real-world and clinical trial data, neuroimaging, biomarker, genomics, transcriptomics, proteomics, and other data (i.e., wearables), have the potential to allow increasingly individualized prediction of trial outcomes based on complex relationships among baseline features, trajectories of decline, drug mechanisms, and clinical and biomarker characteristics across all stages of AD [11,99]. AI technologies may play a crucial role in utilizing multimodal data to accelerate innovations for AD trials [99]. However, there are several challenges for clinical trials in AD drug combinations from a regulatory science perspective. For example, they lack well-established regulatory

guidelines to determine which types of preclinical data support potential clinical trial testing for candidate drug combinations in AD domains. The FDA Modernization Act 2.0 is removing a requirement to use animal studies as supporting preclinical data for future clinical trial testing [100]. However, we still lack well-established human cell-based or brain organoid models to test the complex mechanisms-of-action for drug combinations in human brains. Although combining AI technologies with existing big data (including clinical, biomarkers, and multi-omics) offer alternative approaches, these models are still in their early stages and require more validation before clinical use in regulatory processes and future approvals for drug combinations in AD. Collaborations among academics, industry, and governments will be essential to accelerate development of effective combination therapies for AD in the future.

8. Challenges, perspective and conclusion

The AD/ADRD drug discovery and development community is well-positioned for the emerging development of combination therapies. However, combination therapy development is also challenged by the vast multitude of available drug pairs, complex disease biology, myriad endophenotypes, lack of well-characterized experimental models to validate the preclinical efficacy of combinations, and regulatory hurdles for clinical use.

The challenges for AI-assisted drug combination design for AD/ADRD are distinct from general drug discovery. Where much of AI in traditional drug discovery has access to vast biomedical datasets, the drug combination domain in AD is characterized by data scarcity, lack of high prevalence of successful drug combinations, and lack of knowledge regarding a drugs ability to cross the blood-brain barrier (BBB). The success of AI is critically dependent on high-quality data, a problem that is uniquely acute for drug combinations for which datasets are small and rarely published. Although synthetic data effectively improve model performance in a cost-effective training solution, the unregulated dissemination of synthetic data may lead to the AI autophagy phenomenon [101]. In addition, it still lacks highly reproducible preclinical models to validate the effectiveness of drug combinations in AD/ADRD. The development of fundamentally different AI strategies and validation frameworks is urgently needed to address data sparsity and multimodal data, resulting in accelerated prediction of drug combinations in the AD/ADRD domain. For instance, the community must develop public benchmark datasets with high scientific rigor containing AD/ADRD-specific drug combination data from both preclinical or clinical platforms.

AI can streamline this process by offering innovative models to systematically prioritize potential drug combinations for further experimental and clinical trial testing. However, there are several major challenges in this application of AI as well. For example, we lack large training datasets and benchmark drug combination datasets in the AD field to train and validate classic machine learning or deep learning models before experimental or clinical testing. In addition, traditional ML/DL-based "black box" models have been challenged to predict drug combinations due to the lack of strong biological rationale underlying disease biology. *In silico* network medicine approaches have already offered a promising computational framework (termed "interpretable AI") to identify novel insights to accelerate rational drug combination design, such as specifically targeting multiple endophenotypes or co-pathologies underlying disease biology. These innovative methodological advances have raised the possibility of moving beyond the "one-drug, one-target" paradigm and exploring the "multiple-drugs, multiple-targets" possibilities offered by simultaneously perturbing multiple disease pathways of AD/ADRD, while minimizing potential adverse drug-drug interactions. If broadly applied, these AI and *in silico* network medicine tools will accelerate the development of effective drug combinations for Alzheimer's disease and other complex neurodegenerative diseases as well.

CRediT authorship contribution statement

Feixiong Cheng: Writing – review & editing, Writing – original draft, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Zhendong Sha:** Writing – review & editing, Writing – original draft, Validation, Investigation, Formal analysis, Data curation. **Yadi Zhou:** Writing – original draft, Validation, Formal analysis. **Yuan Hou:** Writing – original draft, Validation, Formal analysis, Data curation. **Pengyue Zhang:** Writing – original draft, Validation, Formal analysis, Data curation. **Andrew A. Pieper:** Writing – review & editing, Formal analysis, Data curation. **Jeffrey Cummings:** Writing – review & editing, Validation, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Feixiong Cheng reports financial support was provided by National Institute on Aging. Feixiong Cheng reports financial support was provided by Alzheimer's Drug Discovery Foundation. Feixiong Cheng reports a relationship with National Institute on Aging that includes: consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

Funding: This work was primarily supported by the National Institute on Aging (NIA) under Award Number U01AG073323, R01AG066707, R01AG084250, R01AG076448, R01AG082118, R01AG092462, R01AG092591, RF1AG082211, and R21AG083003, R33AG083003, and the National Institute of Neurological Disorders and Stroke (NINDS) under Award Number RF1NS133812, and the Alzheimer's Association award (ALZDISCOVERY-1051936) to F.C. This work was supported in part by the Valour Foundation, the Case Western Reserve University Rebecca E. Barchas, MD DLFAPA Professorship in Translational Psychiatry, the University Hospitals of Cleveland Morley-Mather Chair in Neuropsychiatry, and the Louis Stokes VA Medical Center resources and facilities to A.A.P. This work was supported in part by Keep Memory Alive (KMA), NIGMS grant P20GM109025, NINDS grant U01NS093334, NIA grant R01AG053798 and R35AG071476, and the Alzheimer's Disease Drug Discovery Foundation (ADDF) to J.C.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100366.

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