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Harnessing combination therapy: Current treatments, recent advancements, and future directions in Alzheimer's disease

1. Aging and the development of Alzheimer's disease

Advances in modern medicine have increased the human lifespan, leading to more elderly people worldwide [1–3]. Based on data from the United Nations and World Bank, the global population of individuals aged ≥65 years was approximately 750 million in 2023. Notably, about 67-70 % of this population lives in developing countries, representing approximately 500 to 525 million older adults [4]. The United States Census Bureau estimated that over 55 million US citizens were over the age of 65 in 2020, making up almost 17 % of the US population [5]. As the population ages, the prevalence of age-related conditions (eg, type 2 diabetes, cardiovascular diseases (CVDs), cancers, and neurodegenerative disorders is expected to increase [2,3]. Alzheimer's disease (AD) is among the top contributors to disability and mortality in the elderly, with an estimated 7.2 million US citizens age 65 and over living with AD dementia as of 2025 [6]. Without major medical innovations to prevent or cure AD, this number is projected to increase to 13.8 million by 2060 [6].

Aging is a universal process resulting in progressive and irreversible decline throughout the entire body [7]. Throughout life, organisms decline at molecular and cellular levels in response to various stressors including genomic instability, epigenetic alterations, loss of proteostasis, mitochondrial dysfunction, and cellular senescence [7]. In the brain, cerebral atrophy, white and grey matter degradation, and neuropathological protein accumulation (including amyloid-β [Aβ] plaques and tau tangles) gradually manifest throughout aging [8–11]. These aging-associated pathological changes lead to the development of cognitive decline that may manifest as reduced processing speed, reasoning, episodic memory, and spatial visualization [12]. Moreover, aging-associated changes to the brain increase the risk for the development of AD [6,11]. Additional aging-related effects, including chronic inflammation, impaired autophagy, vascular dysfunction, and synaptic loss, contribute to the development and progression of AD development [1]. The recent and major advances in geroscience research will most probably unveil new targets. Loss of neurons in the cerebral cortex and hippocampus, accumulation of Aβ plaques, and neurofibrillary tau tangles are the hallmarks of AD, leading to neuronal dysfunction, impaired memory, and reduced cognitive function [7,13].

Based on growing understanding of the multifaceted dysfunctional biologic processes contributing to the development of AD, combination therapies targeting more than 1 of these interrelated causes may provide the greatest opportunity for slowing the progression of AD [14]. Combination therapy strategies targeting key pathways in a synergistic or additive manner may potentially improve memory, attention, and reasoning compared with monotherapy [15]. Although current combination or coadministration approaches do not halt the progression of AD, they may potentially offer an orthogonal approach to managing symptoms and delaying disease progression [16]. The current AD drug development pipeline includes approaches leveraging pharmacodynamic combinations, pharmacokinetic combinations, and combinations aimed at enhancing penetration across the blood brain barrier [17]. As of June 2025, there are at least 10 clinical trials actively evaluating combination therapies in AD (Table 1). With the regulatory approval of anti-amyloid monoclonal antibodies (mAbs) and their integration into clinical practice, it is anticipated that future trials of putative therapies will need to consider the opportunities and challenges associated with investigating coadministration to patients on a background therapy with mAbs [17].

1.1. Current treatment landscape

Memantine (a N-methyl-D-aspartate receptor [NMDAR] antagonist) and the cholinesterase inhibitors (ChEIs) rivastigmine, galantamine, and donepezil have shown benefits in maintaining or improving cognitive function, at least temporarily [27]. One of the most studied combination therapies for AD is the concurrent use of memantine and ChEIs, which has demonstrated a decreased rate of cognitive decline and reduced severity of anticipated neurobehavioral symptoms (such as aggression) compared with ChEI monotherapy [28]. However, such combinations primarily address the symptoms of AD rather than addressing the underlying biology associated with the progression of the disease [27,28].

More recently, 2 anti-Aβ mAbs (lecanemab-irmb [29] and donanemab-azbt [30] have received full FDA approval as treatments for AD, with additional approvals either granted or under consideration in other regions, including the EU, Japan, China, South Korea, Israel, Australia, Brazil, and Mexico [31,32]. While both mAbs are associated with approximately 30 % slowing of clinical decline and corresponding clearance of amyloid plaque [16,33–35], the need to target other biological process (eg, neuroinflammation, autophagy, mitochondrial or metabolic dysfunction), as well to augment the clinical efficacy, remains.

1.2. Combination strategies and novel treatment approaches in AD

Remarkable results with combination therapies for the treatment of several chronic diseases including neurological conditions, CVD, oncology indications, and metabolic disorders have been noted [33]. Because of the complex nature of AD, upcoming combination therapies

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Table 1
Ongoing and recent clinical trials investigating combination therapies in AD.

Trial	Phase	Population	Treatments	Status	Results
SToMP-AD [18] NCT04685590	2 Randomized Controlled Double-blind	Patients aged ≥60 years with amnestic mild cognitive impairment or early AD	Senolytic therapy (dasatinib + quercetin)vs placebo	Active/not recruiting	Primary completion projected: January 2028
Study 202[19] NCT06602258	2 Randomized Controlled Double-blind	Early AD	E2814 (anti-tau + anti-Aβ) + lecanemabvs placebo + lecanemab	Recruiting	Primary completion projected: August 2027
MET-FINGER[20] NCT05109169	2 Randomized Controlled Double-blind	At risk of dementia	Metformin + FINGER 2.0 lifestyle interventionvs self-guided intervention	Recruiting	Primary completion projected: June 2027
ADEPT-1[21] NCT05511363	3 Randomized Controlled Double-blind	Patients aged 55-90 with possible or probable AD and ≥2 month history of psychotic symptoms	KarXT (xanomeline + trospium chloride) vs placebo	Recruiting	Primary completion projected: October 2026
NCT04570644[22]	1/2 Randomized Open-label	AD	ALZT-OP1a + ALZT-OP1b	Completed in January 2021	
NCT01872598[23]	3 Randomized Controlled Double-blind	Patients aged ≥50 years with AD dementia	Masitinib + cholinesterase inhibitor (donepezil, rivastigmine or galantamine) and/or memantine vs placebo	Completed in December 2020	Dubois B et. al. *Alzheimer's Res Ther* 2023
PEGASUS[24] NCT03533257	2 Randomized Controlled Double-blind	AD	Sodium Phenylbutyrate + Taurursodiolvs placebo	Completed on November 6, 2020	Arnold SE, et al. *Alzheimers Dement (N Y)*. 2024;10(3):e12487
NCT06996730 [25]	2/3 Double-blind Placebo-controlled Double-dummy	Patients with PSEN1 E280A mutation and non-randomized, placebo-treated non-carriers from the same kindred Autosomal-dominant AD	Donanemab + RG6289	Not yet recruiting	Primary completion is projected for December 2030
NCT06602258 [19]	2 Placebo-controlled Double-blind Parallel group Dose-finding	Early AD	Lecanemab + E2814	Active/not recruiting	Primary completion is projected: July 2026
NCT06957418 [26]	2 Platform trial Randomized	Late preclinical or early prodromal AD	Tau-directed therapies, alone or in combination with donanemab	Not yet recruiting	Primary completion projected: August 2028

may serve to address multiple core features, copathologies, and nonspecific symptoms [16]. Given the key roles of other aging-related processes in the pathogenesis of AD, there is a strong rationale for combining agents that address different mechanisms as a means of achieving a more comprehensive impact on the disease process. Current strategies for the management of chronic metabolic diseases like diabetes, a risk factor for the development of AD [36], include multimodal approaches, such as simultaneous lifestyle and pharmacological interventions [37]. Glucagon-like peptide-1 (GLP-1) receptor agonists, including semaglutide, are approved in combination with diet and exercise to improve glycemic control and to reduce the risk of cardiovascular and renal complications in individuals with type 2 diabetes [38]. GLP-1 has established roles in systemic inflammation, vascular health, and microglia/astrocyte homeostasis [39], making it an attractive therapeutic target in AD, with data for liraglutide in mild to moderate AD [40] supporting the ongoing Phase 3 evoke study of semaglutide in early AD. The pleiotropic effects of this class of agents provide a strong rationale for considering GLP-1 receptor agonists as potential components of combination regimens for AD [39]. Moreover, because lifestyle has an impact on metabolic disease management [37] as well as AD onset and progression [41], ongoing studies such as MET-FINGER are investigating the effects of the anti-hyperglycemic agent metformin and targeted lifestyle changes as a potential disease-modifying treatment in AD [42]. Recent research work on brain stimulation techniques could lead to novel therapeutic approaches in the field.

Drug repurposing provides an important opportunity to leverage the known safety and pharmacokinetic profiles of existing drugs previously developed for 1 indication and explore their efficacy for new indications [16]. For example, the FDA recently approved a combination therapy of xanomeline and trospium chloride for the treatment of schizophrenia, representing the first approved antipsychotic with a cholinergic mechanism of action [43]. Researchers have indicated this combination therapy may be effectively repurposed for AD, with an ongoing Phase 3 clinical trial assessing the efficacy of combining xanomeline and trospium chloride to treat the neuropsychiatric symptoms of AD (ADEPT-1; NCT05511363) [43]. Artificial intelligence (AI) models based on real-world data, animal studies, and drug databases may be leveraged to identify prospective therapeutics and repurpose drugs for AD [16].

1.3. A comprehensive perspective on combination therapy for AD: key considerations

This edition of The Journal of Prevention of Alzheimer's Disease (JPAD) addresses contemporary issues in advancing the exploration of combination therapy for AD. The first article provides a foundation for the edition through an overview of various types of combination therapies for treatment of AD as well as potential challenges for consideration [44]. The field has been conducting combination and coadministration studies for decades, exploring putative symptomatic and/or disease-modifying therapies added to a background of stable standard of care (SOC) treatment with symptomatic agents (i.e., acetylcholinesterase inhibitors alone or with memantine). The recently approved anti-amyloid mAbs, with their effects on slowing the rate of

decline and changing canonical biomarkers in AD, elicit new considerations for designing trials of combination regimens that incorporate mAbs. The second article provides a discussion of considerations specifically related to coadministration or combination therapy with mAbs, including clinical trial design, statistics, biomarkers, and operational implementation [45]. Reflecting the burgeoning use of AI in drug development, this edition also includes an article addressing the use of AI in the selection of putative combination therapies for nonclinical and/or clinical exploration [46]. Statistical considerations for combination therapy trials are addressed in 2 papers providing frequentist and Bayesian approaches for considerations in the design and conduct of combination therapy trials for AD [47,48].

The penultimate article in this edition focuses on the potential role for combination of lifestyle intervention with pharmacologic approaches as a multifaceted approach to treatment [49]. The final article addresses opportunities and challenges associated with the development of combination therapy with repurposed therapies [50].

1.4. A vision for the future of treatment for AD

While combination therapy approaches offer opportunities for significant improvement in patient outcomes, potential challenges exist to achieving their successful investigation in clinical research and implementation in clinical practice [14]. A key unanswered question relates to the optimal trial infrastructure and the potential role of different trial designs. Adaptive trial designs such as platform trials or response-adaptive randomization could offer flexibility to allocate participants to promising treatment arms in real time based on the data from the ongoing AD trials, similar to application in other areas (eg, oncology) [14]. Notwithstanding, the ongoing DIAN-TU, Alzheimer Tau, and MET FINGERS trials provide excellent opportunities to build upon the experience of these investigators in executing such studies [42,51–53]. Another salient question relates to the utility of AI and machine learning in drug development trials. Although the use of these tools has developed rapidly and is expanding, there are still challenges, such as a lack of large training sets 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 [46]. Indeed, further development is still needed in this area prior to any successful implementation.

Increasing adoption of anti-amyloid mABs in clinical practice will present an opportunity for the exploration of combination therapy with novel therapies. In such scenarios, several key issues must be addressed to enable effective trial design. These include defining strategies for enrolling patients already receiving mABs and determining how best to assess the safety and efficacy of add-on therapies administered alongside existing therapies. Additional considerations involve the optimal timing of treatment for introducing a novel agent following mAB initiation, identifying determinants of treatment response, evaluating the impact on clinical and biomarker assessments, and thoroughly interrogating the safety and tolerability of combination regimens. Thus, the next phase of development of combination therapy for AD will require significant investments, painstakingly building a new body of evidence, new ways of thinking about the disease, and the flexibility to adapt approaches as we learn new information [14].

Beyond the scientific and medical rationale supporting combination therapy for AD, there are very important operational considerations that will determine the feasibility of its implementation in real-world practice. One such consideration is determining the optimal stage in drug development to evaluate combination therapy. A common strategy is to first establish a minimal profile (defined as the essential characteristics of a therapeutic agent such as efficacy, safety, target engagement) that justify its inclusion in a combination regimen. However, there is also an opportunity to explore de novo evaluation of agents specifically within the context of combination therapy, which may reveal synergistic effects not evident in monotherapy trials. Another key unanswered question relates to repurposed drugs (eg, off patent). While these drugs offer valuable opportunities to develop effective combination regimens, it remains a challenge to garner the financial support to move forward with these agents given the perceived lack of commercial opportunity. Additionally, while current research efforts primarily focus on therapeutic regimens that modulate AD symptoms or alter disease progression, there is a compelling opportunity to investigate the use of combination therapy for AD prevention, a critical area of unmet need. Finally, a key goal of current clinical trials is obtaining regulatory approval; however, there are other factors beyond clinical evidence and approval that impact the incorporation of a treatment regimen into clinical practice. The overarching regulatory environment is a critical consideration that directly impacts drug development and, because regulatory requirements can vary across different countries and regions, they have a direct and long-term impact on shaping the AD therapeutic landscape, associated costs, and patient access to treatment. While the unaddressed questions above are beyond the scope of this editorial, they are integral to advancing treatment and will determine the environment in which future therapies will be developed.

Conflicts of interest

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

HMF provided consultation to Alector, Inc, LifeWorX, and TheKey. HMF is a chairman, independent data management committee at Alector, Inc and a member of clinical advisory board at ProMis Neurosciences Inc and advisor at LifeWorX and TheKey. HMF is an observer and on board of directors at Therini Bio Inc and ADmit Therapeutics SL.

JT declares receipts of grants or contracts from ReGenlife, Anavex Life Sciences Corp and Ariana Pharmaceuticals and owns stock options for ReGenlife. JT provided consultation and received honoraria from ReGenlife for lectures, presentations, speakers' bureaus, manuscript writing or educational events. JT participated in a Data safety Monitoring Board or Advisory Board for ReGenlife, Anavex Life Sciences Corp and Ariana Pharmaceuticals.

BV reports a relationship with the IHU HealthAge (Research National Agency, France 2030) Toulouse University Hospital and is an investigator in clinical trials sponsored by several industry partners. BV has served in the past 3 years as SAB member for Biogen Inc, Alzheon Inc, Norvo Nordisk Inc, Eli Lilly and Company, Eisai Inc, Roche, JNJ Ltd without personal compensation. BV is part of the Clinical Trials on Alzheimer's Disease (CTAD) Organizing Committee and the Journal of Prevention of Alzheimer's Disease (JPAD) editorial board.

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Howard M Fillit: Writing – review & editing. **Jacques Touchon:** Writing – review & editing. **Bruno Vellas:** Writing – review & editing. **Laura K Nisenbaum:** Conceptualization, Writing – review & editing. **Aaron H Burstein:** Conceptualization, Writing – review & editing.

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Howard Fillit reports a relationship with Therini Bio Inc that includes: board of directors membership. Howard Fillit reports a relationship with Alector Inc that includes: chairman, Independent Data

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Jacques Touchon reports a relationship with REGEnLIFE that includes: consulting or advisory, equity or stocks, funding grants, and speaking and lecture fees. Jacques Touchon reports a relationship with Anavex Life Sciences Corp that includes: consulting or advisory and funding grants. Jacques Touchon reports a relationship with Ariana Pharmaceuticals that includes: consulting or advisory and funding grants.

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Special Article

Alzheimer Combination Therapies: Overview and Scenarios

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ABSTRACT

Progress in understanding the complexity of Alzheimer's disease informs the search for combination therapies that can successfully prevent or substantially slow the progression of the disease. Anti-amyloid monoclonal antibodies are the first approved disease targeted therapies; they slow disease progression by approximately 30 %. Building on these agents in add-on therapies is one avenue to designing combination treatments. Development of combination drugs consisting of two or more novel interventions is an alternate pathway for combination treatment development. Combination therapies can involve small molecule drugs, biological agents, devices, stem cells, gene therapies, lifestyle interventions, or cognitive training. Nonclinical assessment of drug combinations may involve animal models or new approach methodologies such as induced pluripotent stem cells or organoids. Phase 1 trials are required to characterize each member of a novel combination. Phase 2 trials may use a 2-by-2 factorial design comparing each drug to placebo and the drug combination. In Phase 3, comparison of the novel combination to standard of care may be sufficient or more complex designs may be required. Targets for combination therapies beyond amyloid-related processes include tau abnormalities, inflammation, neurodegeneration, and co-pathologies such as alpha-synuclein and TDP-43. The choice of combination therapies will depend on the strength of the information regarding the target, biomarkers to guide clinical trials, and a candidate agent with the appropriate mechanism of action. Computational strategies based on network analysis of disease and drugs, validation in non-clinical models, and use of real-world data may facilitate prioritization of candidates for combination treatments.

Combination therapy is the necessary response to recognition that Alzheimer's disease (AD) is a complex multifaceted disorder with a plethora of contributing processes[1,2]. In addition to the core abnormalities of amyloid plaques and neurofibrillary tangles, pathophysiological abnormalities including Inflammation and neurodegeneration as well as co-pathologies such as alpha-synuclein and TAR DNA protein 43 (TDP-43) represent pathologies that contribute to the progression of AD and are potential targets for therapeutic intervention[3].

The need for combination therapy is further amplified by the observation that therapies addressing a single pathology — amyloid plaques — produce 30 % slowing of cognitive decline, leaving 70 % of cognitive decline unaddressed[4,5]. Progress in disease targeted therapies (DTTs) represented by the anti-amyloid monoclonal antibodies (MABs) indicates that intervention in the biological processes of AD is a viable therapeutic endeavor. Similarly, recent observations of antisense oligonucleotides (ASO) reducing RNA transcription of the Microtubule-Associated Protein Tau (MAPT) gene to reduce tau protein levels suggest that tau pathways are vulnerable to therapeutic manipulation[6]. Success in DTT development encourages the search for novel combination and add-on therapies to create more efficacious interventions.

Drug development of DTTs is guided by diagnostic, pharmacodynamic, and safety biomarkers. Biomarkers are increasingly available to guide drug development and to report on the pathophysiological impact of treatment in clinical trials[7,8]. Biomarkers may play a role in a variety of contexts of use including diagnosis, identification of risk, provision of prognostic information, measurement of pharmacodynamic effects, generation of predictive information forecasting benefit or harm, use for monitoring of treatment effects over time, or following the safety of treatment[9].

Progress in understanding the neurobiology and complexity of AD, the success in developing DTTs, the need to amplify the efficacy of current DTTs, and the availability of biomarkers to guide clinical trials combine to provide the foundation for successful development of

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combination therapies.

Key aspects of advancing combinations treatments that may improve the benefical effects on patient cognition and function involve regulatory considerations, impact of anti-amyloid MABs on trial design, novel designs for combination therapies, statistical analyses relevant to clinical trials of combination therapy, operational issues that emerge when administering at least 2 agents to trial participants (e.g., regimen, formulation, etc.), and strategic considerations when agents of the combination are at different levels of development or are being developed by different companies[1].

Here we provide an overview of types of combination treatments and opportunities and challenges for developing combination therapies for AD. We describe formulation issues associated with combination therapy. We discuss clinical trial designs relevant to assessing combination treatment in different phases of drug development. We discuss the effects of combination therapies on biomarkers and the use of biomarkers in drug development programs for combination treatments. We note the challenges in prioritizing drugs for use in novel or add-on combinations. We emphasize combination DTTs, while noting the wide variety of combination interventions that are feasible.

1. Types of combination therapies

There are a variety of types of combination therapies comprised of the simultaneous administration of two or more interventions with the intent of slowing disease progression or improving symptoms[10]. We describe the principal types of combinations and give examples from AD therapeutics or treatments of other neurodegenerative disorders (NDDs) when they are available (Table 1). We note that each type of combination may require a different development pathway or clinical trial design [11]. Combination therapies seek to increase the pharmacodynamic impact of treatment; in some cases, this is done by adding two or more pharmacodynamically active agents, in others it is accomplished by combining agents that reduce peripheral side effects or peripheral metabolism allowing greater entry of the pharmacodynamically active element into the brain. Combinations could be two or more small molecules, two or more biological agents, or some combination of small molecules and biological therapies. Beyond combinations of drugs, combination therapies may involve devices, stem cells, genes, lifestyle, or cognitive training interventions. In 2025 there were 20 trials involving combinations of drugs. This included trials with two pharmacodynamically active agents, trials with one pharmacodynamically active agent and one to reduce peripheral side effects, and trials with one active agent and one to reduce peripheral metabolism[1].

The US Food and Drug Administration (FDA) Distinguishes between "combination products" and combination therapies. Combination products are entities such as a drug-device combination where the device is required for administration of the drug (discussed below). "Combination therapies" refers to two or more agent administered together[12] .

1.1. Combinations of novel agents

Two or more novel agents may be combined in the drug development process to produce outcomes better than those expected with monotherapy. Efficacy of each element of the combination must be demonstrated during the development process for each of them to be marketed as monotherapy in addition to their use in combination therapy. If one agent is to be introduced first followed by add-on of a second novel agent, the sequence will be determined by pharmacologic, biomarker, safety, and operational factors.

Combination treatment might address amyloid beta protein (Aß) _plus tau, tau plus inflammation, tau plus synaptic plasticity, tau plus neuroprotection or other combinations where each agent is expected to contribute to the pharmacodynamic response[13]. Combinations might also address co-pathologies involving the core pathological changes of

Table 1
Types of combination therapies and examples from Alzheimer's disease or other neurodegenerative disorders or proposed combinations.

Type of Combination	Example
Two or more agents in combination; one or more of the elements may be repurposed	Ciprofloxacin and Celecoxib (NCT06185543) to reduce inflammation; Rotigotine + Rivastigmine (NCT06702124) to augment 2 transmitters (dopamine and acetylcholine)
Add-on of a novel agent to an existing therapy such as a monoclonal antibody	DIAN-TU study in which for patients with symptoms, lecanemab is administered for 6 months and then E2814 or placebo is added on (NCT06602258)
Combination products	Subcutaneous lecanemab administered with an autoinjector (NCT03887455)
Sequential combinations	Proposed combination: anti-amyloid monoclonal antibody to reduce amyloid plaque followed by a gamma-secretase modulator to prevent re-accumulation of amyloid plaques
Single agents that have multiple effects	Rasagiline exhibited neuroprotective, anti-inflammatory, and p-tau effects in a Phase 2 trial (NCT02359552); ExPlas (plasma from exercised individuals) (NCT05068830); multiple plasma proteins to enhance synaptic plasticity and promote neuroprotection; proteostasis agents such as buntanetap/ phenserine may exert effects on multiple proteins including Aß, tau, and alpha-synuclein (NCT06709014)
Traditional medications and remedies	Yangxue Qingnao (NCT04780399); Traditional Chinese Medication
Combinations of an active agent and an agent to reduce peripheral side effects	Xanomeline + Trospium (KarXT; Cobenfy®)(NCT05511363); trospium block the peripheral cholinergic side effects of xanomeline
Combination of an active agent and an agent to reduce peripheral metabolism	Dextromethorphan + Bupropion (NCT04947553)(buproprion blocks peripheral metabolism of dextromethorphan by inhibiting CYP2D6; Auvelity®); dextromethorphan plus quinidine (quinidine blocks peripheral metabolism of dextromethorphan; Nuedexta®)
Combination of agents to enhance blood-brain barrier penetration	Trontinemab (gantanerumab + Brainshuttle™)(NCT04639050); the shuttle interacts with the transferrin receptor to allow passage of gantenerumab across the blood-brain barrier
Combination of a monoclonal antibody and an ultrasound device	Magnetic resonance guided focal ultrasound delivery resulted in local increase in removal of Aß plaques attributed to enhanced blood-brain barrier penetration of the antibody (NCT05469009)
Combination of pharmacotherapy and lifestyle modification	MET-FINGERS (NCT05109169); participants at risk for cognitive decline are randomized to FINGERS intervention vs regular health advice; within the FINGERS arm, those at risk for diabetes are randomized to metformin or placebo
Combination of pharmacotherapy and cognitive stimulation	Participants were treated with pharmacotherapy (rivastigmine) and randomized to cognitive stimulation therapy or standard of care. Those receiving cognitive stimulation benefited more than those receiving only rivastigmine and standard of care[50]
Combination of pharmacotherapy and noninvasive brain stimulation	Repetitive transcranial stimulation is combined with cognitive training during the stimulation period to enhance the effects of either therapy when delivered alone (NCT01504958)

AD — Aß or tau — plus alpha-synuclein or TDP-43[14]. Combination therapies could include combining DTTs with novel cognitive enhancing agents, drugs to treat neuropsychiatric symptoms, or sleep-enhancing/diurnal rhythm agents.

Two active agents of a combination may address the same or overlapping targets. COYA 302, for example, is intended to enhance the anti-inflammatory function of regulatory T cells (Tregs) and suppress the inflammation produced by activated monocytes and macrophages. The combination is comprised of low dose interleukin 2 and abatacept and is being developed for subcutaneous administration for patients with NDDs including frontotemporal dementia (FTD) and AD[15]. The therapeutic hypothesis is that the two agents will have additive or synergistic effects by impacting several elements of the complex inflammatory network.

1.2. Add-on combinations

Add-on therapies have a history in treatment development for AD. Donepezil is a cholinesterase inhibitor approved for treatment of mild to moderate and severe AD. Memantine is an N-methyl-D-aspartate antagonist approved for monotherapy or add-on treatment of moderate to severe AD based on a single monotherapy trial followed by an add-on trial to donepezil[16,17]. The two agents have complementary mechanisms and are commonly used together. These trials represent add-on therapies of cognitive enhancing agents, and, in some cases, synergistic effects may be observed[18]. Nearly all agents in current clinical trials allow the inclusion of participants receiving stable (3–4 months) background standard of care therapy with cholinesterase inhibitors and/or memantine. In such cases the requirement for stable background therapy represents the definition of the control group (e.g., donepezil + placebo) against which the new combination (e.g., donepezil + novel agent).

Namzaric^{R} is a fixed combination of 10 mg of donepezil and 28 mg of memantine. This is a combination of repurposed agents. The efficacy of the donepezil compared to placebo was established in monotherapy trials. In the Namzaric^{R} development program, a single trial of participants on stable doses of 10 mg daily of donepezil were randomized to an add-on of 28 mg of memantine or placebo. Superior efficacy of the combination over donepezil monotherapy was demonstrated and the combination treatment was approved[19]. This is an example of an add-on strategy leading to approved fixed combination based on a single add-on trial.

Combinations of a novel and an approved cognition enhancing agent represent another approach to add-on therapy. Noradrenergic agents may amplify the effects of cholinesterase inhibitors, and one trial design randomizes patients receiving donepezil (a cholinesterase inhibitor) to guanfacine (an α2A adrenergic receptor agonist) or placebo to explore the effects of the combination on cognition enhancement[20].

Add-on combinations will become increasingly common as novel agents are added on to the therapeutic regimen of patients receiving treatment with an anti-amyloid MAB. Lecanemab and donanemab are available by prescription in the US and many other countries. They are indicated for patients with early AD (mild cognitive impairment (MCI) due to AD or early AD dementia) with confirmed amyloid pathology, no excessive cerebrovascular disease as established by magnetic resonance imaging (MRI), and no contraindications to MAB use.

Anti-amyloid MABs produce measurable slowing on global, cognitive, and functional outcome measures of 25 to 40 %[4,5]. Add-on therapies offer the opportunity to further slow disease progression and extend more intact cognitive function for longer periods. An add-on therapy trial would include only patients who met MAB treatment criteria when the MAB therapy was initiated. MAB therapy patients will typically have early AD, be known to be amyloid positive at the time of initiation of the MAB and have limited evidence of cerebrovascular disease. The add-on agent might be developed for monotherapy in patients outside of this narrowly defined range. Anti-amyloid MABs are known to produce amyloid related imaging abnormalities (ARIA) in the first few months of treatment initiation. Most ARIA events are asymptomatic, but a few produce symptoms, and they rarely cause severe injury and death[21,22]. The timing of an add-on intervention must take ARIA into account or risk having ARIA attributed to the novel agent. If the add-on agent has a well-known safety profile without ARIA (i.e., repurposed drugs), then simultaneous initiation of combination therapy can be considered. Anti-amyloid MABs are administered intravenously monthly (donanemab) or twice monthly (lecanemab for the first 18 months) then monthly and the regimen and formulation of a novel add-on must be compatible with adherence to this treatment schedule. Anti-amyloid MAB therapy produces profound changes in AD biomarkers including marked reduction in Aß plaque on amyloid positron emission tomography (PET) and decreased plasma p-tau 181, p-tau 217, and glial fibrillary acidic protein (GFAP)[5,23]. The biomarker profile of the novel agent must be established in monotherapy trials to facilitate interpretation of biomarker changes in the add-on setting. Some patients on MABs do not have complete amyloid clearance and reducing plaque burden to 25 Centiloids or less could be an indication of additional therapeutic response from a co-administered agent. In addition, donanemab is plaque-directed and add-on therapy with agents targeting other species of amyloid may prolong the effects of donanemab or improve the efficacy. An open label lead-in with reduction of plaque amyloid followed by the add-on agent or placebo is a design opportunity to address this type of question. Target engagement biomarkers for the novel treatment might distinguish biomarker effects from those of MABs.

The Dominantly Inherited Alzheimer's Disease Network Treatment Unit (DIAN-TU) and the Alzheimer Tau Platform are platform trials in which novel agents may be added to anti-amyloid MAB regimens (DIAN-TU) or anti-amyloid MABs may be added on to experimental agents (Alzheimer Tau Platform)[24,25]. These platform trials add valuable information regarding simultaneous or staggered introduction of therapies and involvement of participants with and without cognitive impairment.

Combinations to be considered as add-ons to anti-amyloid MABs include anti-tau agents, anti-inflammatory drugs, and synaptic plasticity/neuroprotective agents. Add-on therapies could involve MABs directed at tau aggregates, alpha-synuclein, or TDP-43 as well as other central nervous system (CNS) targets relevant to AD[26,27]. Additionally, add-on treatments intended to reduce the risk of ARIA and potentially expand the population of patients eligible for MABs may represent opportunities for exploration.

1.3. Combination products

The FDA defines a "combination product" as: 1) a product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are combined or mixed and produced as a single entity; 2) two or more separate products packaged together in a single package and comprised of a drug and device, a device and biological product, or a biological and drug; 3) a drug, device, or biological product packaged separately that is intended for use only with an approved specified drug, device, or biological product; or 4) any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product[28].

Currently, lecanemab is being developed for subcutaneous administration with an autoinjector. This combination of drug and device represents a combination product being assessed for AD therapeutics. Similar approaches for other therapies are anticipated.

1.4. Sequential combinations

Sequential combinations are treatment regimens in which one

specified drug is used and stopped and is then followed by another prespecified drug. For example, an anti-amyloid MAB may be stopped when Aß plaques are no longer detectable by amyloid PET. To extend the period of treatment-related amyloid clearance (TRAC) in the brain, a gamma secretase modulator might be used as a follow up therapy to prevent plaque re-accumulation[29]. This regimen represents an example of a sequential combination aimed at a single therapeutic target, Aß plaques. Sequential treatments could also be directed to non-plaque amyloid species such a protofibrils or oligomers.

1.5. Single agents that have multiple effects

Drugs that are posited to have effects on multiple key nodes of the AD pathophysiological network might be considered as "combinations in a pill". In experimental settings, buntanetap, for example, reduces amyloid precursor protein, tau, alpha-synuclein, and other toxic proteins by suppressing mRNA translation[30]. Interference with proteostasis and the aggregation of multiple types of protein might suppress common pathologies and co-pathologies in AD and be applicable across NDDs.

In a review of the 2025AD drug development pipeline, 4 agents were identified as multi-targeted molecules[31].

1.6. Traditional medications and remedies

Indigenous culture medications such as Indian, Korean, and Chinese traditional medications as well as medications from other healing traditions are usually combinations of herbs or other plants thought to have medicinal effects and represent combination therapies[32]. Yangxue Qingnao is a Chinese traditional medication comprised of an herbal mixture and shown in animal models and preliminary studies in humans to enhance brain circulation and increase Aß degradation in the liver [33]. Yangxue Qingnao is being assessed in a Phase 2 study of patient with mild to moderate AD (NCT04780399).

Bu-Wang San is a Chinese traditional medication that has been assessed for potential multimodal impact[34]. Multiplatform metabolomic studies indicated a primary impact on amino sugar and nucleotide sugar metabolism, as well as on glycine, serine, and threonine metabolic pathways.

Marketing of traditional medications often preceded the development of modern regulatory standards, and not all vendors have advanced quality control standards to ensure product identity, purity, composition, batch consistency, and safety[35,36]. Awareness of these issues is important if traditional medications are being taken by patients who may add on novel therapies to current regimens or participate in trials of experimental agents.

1.7. Combinations of an active agent and a drug to reduce peripheral metabolism of the active agent

One means of optimizing the pharmacodynamic effect of an active agent is to use a combination of approach in which one element of the combination suppresses the peripheral metabolism of the active ingredient. This allows higher peripheral levels and an enhanced ability of the active agent to cross the blood brain barrier (BBB) to achieve greater central effects. Dextromethorphan, for example, a centrally active N-methyl-D-aspartate antagonist and sigma-1 agonist, is peripherally metabolized by cytochrome P450 (CYP) 2D6 liver enzymes. Co-administration of a CYP 2D6 inhibitor allows higher peripheral and higher central levels. The combination of dextromethorphan and quinidine capitalizes on the 2D6 inhibitory properties of quinidine to achieve higher central dextromethorphan levels. This combination is approved, as Nuedexta®, for the treatment of pseudobulbar affect[37]. This combination was also used in preliminary studies to reduce agitation in AD [38].

AXS-05 is a combination of dextromethorphan with bupropion. Bupropion is a CYP 2D6 inhibitor that leads to elevated peripheral and central levels of dextromethorphan. The combination of bupropion and dextromethorphan is approved (as Auvelity ®) for the treatment of major depression and is being assessed for treatment of agitation associated with AD dementia[39].

The combination of two agents, one with central activity and one intended to reduce the peripheral metabolism of the active agent, may have a safety profile that combines adverse events arising with each agent. Vigilance when developing this kind of combination is warranted. If the adverse event profile of each agent is known, checklists of treatment emergent adverse events of special interest may be used for side effect characterization during development.

With this type of combination, co-development of the two agents meets the Food and Drug Administration (FDA) criteria for co-development. Co-development requires that the combination is intended to treat a serious disease or condition; there is a compelling rationale for use of the combination; preliminary clinical data support use of the combination; and there is a compelling reason that the agents cannot be developed individually for this indication[40]. The FDA co-development guidance applies to two or more unmarketed compounds and does not specifically address the development of repurposed agents.

1.8. Combinations of an active agent and a drug to reduce peripheral side effects of the active agent

Another type of combination directed to optimizing central effects of an active agent is to co-administer an agent that blocks peripheral side effects that may accompany treatment. For example, the M1M4 agonist xanomeline is associated with peripheral cholinergic effects. In the development program of Cobenfy®, trospium was co-administered to block the peripheral cholinergic effects of xanomeline, allowing increased central exposures to be achieved with acceptable side effects. This combination is approved for treatment of adult with schizophrenia and is in clinical trials for treatment of AD-related psychosis based on observations suggesting that the xanomeline reduces psychotic and agitated behavior in AD[41].

Combination agents of this type may exhibit side effects associated with both agents.

Since these agents are not intended to be used alone for the indication for which they are being developed, FDA guidance for co-development or two or more unmarketed investigational drugs defines the expectations of the FDA for the development program, although this guidance applies to novel agents and not specifically to new uses of repurposed agents[40].

1.9. Combination agents designed to enhance blood-brain barrier penetration

Many drugs are excluded from the CNS environment by the BBB. Barrier mechanisms exclude large molecules (greater than 500 Daltons), hydrophilic drugs, drugs that are metabolized by CYP450 enzymes found in endothelial cells and surrounding astrocytes, and drugs excluded by specific efflux transporters such as P-glycoprotein (P-gp) [42,43]. Combining a large molecule with a receptor mediated BBB transport mechanism may allow entry of agents typically excluded from the brain such as MABs.

Trontinemab is a bispecific fusion molecule comprised of a "cargo" monoclonal antibody (previously being developed as gantenerumab) and a transferrin receptor ligand that interacts with the receptor to allow the MAB to be transported through the BBB via transcytosis and released into the CNS[44]. Trontinemab circulating in the bloodstream binds via the Brainshuttle® to the transferrin receptor on the luminal surface of endothelial cells that comprise the BBB. Receptor binding leads to endocytosis of gantenerumab and release through exocytosis into the intracerebral space. This results in better BBB penetration with higher brain concentrations and lower plasma concentrations. Brain-Transporter™ similarly uses the transferrin receptor to enhance BBB

penetration of MABs. Transferrin receptors are not confined to the brain and vigilance for off target effects is warranted with this approach. Trontinemab is in current clinical trials as a DTT for treatment of AD. If successful, the transferrin receptor technology may be used to enhance brain entry of treatments for non-AD NDDs.

1.10. Combination pharmacotherapy and focused ultrasound

Temporary opening of the BBB can be achieved with focused ultrasound. This technology is being explored in a variety of therapeutic areas including AD, Parkinson's disease, and glioblastoma[45]. The ability of focused ultrasound to temporarily open the BBB creates an opportunity for a drug-device combination with increased CNS penetration facilitated by ultrasound treatment. In a preliminary study of patients with AD receiving aducanumab, focused ultrasound to one hemisphere was associated with greater amyloid plaque removal from that hemisphere compared to the homologous region in the contralateral hemisphere[46]. This study suggests that temporary opening of the BBB by focused ultrasound allowed greater entry of the therapeutic anti-amyloid MAB and greater removal of the amyloid plaque drug target. It is important to demonstrate the safety of long-term use of focused ultrasound as a drug-device combination for the approach to be widely implemented.

1.11. Combination pharmacotherapy and lifestyle intervention

Increasing evidence suggests that lifestyle interventions including physical exercise, healthy nutrition, and control of cardio-cerebrovascular risk factors can improve brain health and delay the onset or slow the progression of cognitive decline[47]. These beneficial activities can be combined with any therapeutic intervention including cognitive enhancing agents, anti-amyloid MABs, or emerging therapies.

One example of a combined lifestyle and pharmacotherapy intervention is the MET-FINGERS study[48]. In this clinical trial, patients are randomized to the FINGERS lifestyle intervention or usual care. Within the FINGERS arm of the trial, those patients for whom metformin is indicated (have risk indicators of type 2 diabetes) are re-randomized to active treatment with metformin or placebo. This design will allow study of the additive or synergistic effects of lifestyle changes and metformin therapy.

1.12. Pharmacotherapy plus cognitive stimulation combinations

Cognitive stimulation such as memory training, decision rehearsal, deficit compensation, and real work practice can benefit patients with MCI or early AD dementia[49]. A combination of cognitive stimulation with pharmacotherapy may enhance the beneficial response. One trial included treating all participants with rivastigmine and randomizing them to either standard of care plus rivastigmine treatment or cognitive stimulation plus rivastigmine. The cognitive intervention included at least 90 min per week of activities directed by a neuropsychologist for a 2-month interval. Patients receiving the combination therapy had significantly better outcomes on cognitive, mood, and functional measures[50].

1.13. Combination noninvasive brain stimulation and cognitive training

Noninvasive brain stimulation plus cognitive training represents an opportunity for device-cognitive training combination therapy. These studies combine regular noninvasive brain stimulation with cognitive training administered simultaneously with the device application. Preliminary evidence suggests a benefit in amnestic MCI and AD dementia [51,52] although not all studies of this combination have shown cognitive benefits[53].

2. Formulations of combination therapies

Considerations of drug formulation may become more complex in the development of combinations compared to monotherapy drug delivery. Patient and caregiver burden associated with combination therapy regimens can be mitigated by considering the administration and adherence requirements for all medications being prescribed for the patient. Taking one pill with two elements or two pills once or twice a day is a convenient mode of administration. Packaging of oral medications must consider the fact that individuals with AD or caring for someone with AD and who are opening bottles of tablets or peeling blister packs to access medications will likely be older may encounter difficulties if they have arthritis, neuropathy, or other physical limitations. Smart pill dispensers, autoinjectors, digital adherence monitors, smartphone reminders, and telehealth availability may reduce the burden of monotherapy and combination therapy on patients and caregivers. More complex regimens such as intravenous infusions once or twice monthly, intrathecal administrations, subcutaneous injections, intramuscular injections, and intranasal administration could adversely affect patient acceptance and adherence. Approaches for promoting patient convenience, encouraging adherence, and assessing acceptability of combination formulations may assist in advancing combination drugs from trials to clinical use. If the patient is on an existing agent such as a MAB and a second agent is to be added, planning for convenience and adherence will facilitate successful treatment initiation. MABs are currently administered intravenously; subcutaneous formulations are being investigated. The FDA has developed human factors guidance for combination product development addressing issues of convenience, safety, and risk[54].

3. Combination therapy development

Here we consider aspects of the development of combination therapies. Recommendations are made based on published studies, mechanistic information, and experience with other development programs. Judgments about the best possible trial design and development program will vary depending on the combination of molecules of interest, the information needed to advance the program, and guidance from regulatory authorities.

3.1. Non-clinical studies

Assessment of combination treatments can begin in the non-clinical phase of development with studies in animal models of AD or New Approach Methodologies (NAMs) that model aspects of human AD (this initial step is shown in Figures 1-4). The FDA Road Map to Reducing Animal Testing in Preclinical Safety Studies suggests that developers may rely increasingly on NAMs to provide guidance for safety and first-in-human exposures[55]. Animal models of AD have provided systems in which to study the pharmacodynamic impact of treatment on specific molecular pathways that can be reproduced in transgenic animals. These model systems do not recapitulate the complexity of human AD and do not predict trial participant responses to novel medications[56]. Relatively few non-clinical experiments involving combination therapy for AD have been reported. Tested combinations have not succeeded in being advanced to human studies[57,58]. Animal models have contributed importantly to observations regarding pharmacologic toxicity as well as dosing strategies for Phase 1 studies. Non-clinical animal models may provide insight into add-on therapies where rodents receiving anti-amyloid MABs could be exposed to a novel and-on therapy or placebo.

When both elements of the combination are new molecular entities (NMEs), FDA encourages a complete non-clinical evaluation of each NME (e.g., genetic toxicology; pharmacology; safety pharmacology; pharmacokinetics (PK); absorption, distribution, metabolism, excretion (ADME); toxicity; reproductive and developmental toxicity;

carcinogenicity). The agency also recommends the assessment of the combination in non-clinical studies. If the two drugs or biologics will be used only in combination, it is possible that it may be sufficient to conduct toxicology studies only on the combination without assessing each NME independently[59]. Animal studies of efficacy of the combination are not generally needed for the novel agents if they are intended for monotherapy and possible add-on use.

When an NME is to be used in combination with a previously marketed drug or biologic as in the case of add-on therapy with anti-amyloid MABs, the FDA recommends that non-clinical studies be conducted on the NME. Such studies will already have been completed for the previously marketed compound. In chronic conditions such as AD, the FDA recommends that a sponsor conduct a bridging study of up to 90 days with the combination therapy in the most appropriate species[59]. As noted with combinations of two or more novel agents, animal studies of efficacy of the combination are not expected. The final details of the planned non-clinical studies should be reviewed with the FDA or other regulatory agencies to ensure their appropriateness[60].

If one of the agents in the combination is repurposed, electronic medical records (eMRs) can be reviewed to determine if pharmacoepidemiologic agent supports clinical efficacy by showing a decreased incidence in those exposed to the agent compared to those on other agents given for similar periods of time for the same indication[61]. In some cases, trial emulation may be possible with matching of exposed and unexposed groups to assess an outcome that is trial-relevant[62].

3.2. Phase 1 of a combination therapy development program

Combination therapy may pursue a co-development program where the drugs will always be used together and there is a compelling reason that the drugs cannot be developed independently[40]. Combination therapies can also be studied in programs where each efficacious agent may eventually be used independently, and the sponsor is interested in determining the benefit of the proposed combination for efficacy, safety, or commercial purposes.

Phase 1 of a program focused on development of two agents that may eventually be used independently as well as the combination of these two agents will be characterized by standard assessments expected in first-in-human studies including determination of the maximum tolerated dose (MTD), the nature of the dose limiting toxicity (DLT), and PK parameters. Determination of a dose-response for measures such as biomarkers will provide important guidance for dosing in Phase 2. The effects of food on PK characteristics and possible drug interactions should be determined for each agent. CNS penetration should be assessed and the plasma: cerebrospinal fluid (CSF) ratio determined. In most cases, if small molecules are being developed, participants are healthy volunteers. If one or more of the agents being studied is a biologic such as a MAB, trial participants may have AD.

If one agent of the combination is marketed and an add-on approach is anticipated, Phase 1 will have been completed for the marketed agent and Phase1 can focus on the novel agent.

Studies of the drug combination should be pursued in Phase 1 if drug interactions or additive or synergistic toxicities are anticipated[12]. If there suspected interactions or additive toxicity, combination studies will be required whether both agents are novel, or one is marketed and one novel.

Open label assessments of combination therapies to build confidence in safety and collect directional efficacy information may be considered in Phase 1b studies. This course was taken in the SToMP-AD program assessing the combination of dasatinib and quercetin for treatment of AD [63]. An important learning from this trial and a demonstration of the importance of preliminary studies of this type was that quercetin was undetectable in CSF suggesting that it was not contributing to the potential efficacy of the senolytic combination[64].

3.3. Phase 2 of a combination therapy development program

A 2-by-2 factorial study with four arms comprised of drug A, drug B, the combination AB, and placebo is a preferred Phase 2 design (Figure 3). This design allows exploration of the contribution of each drug to the efficacy of the combination treatment, facilitates assessment of the efficacy and safety of each of the component drugs, and provides insight into any drug interactions or additive toxicity. Early assessment of the combination has an advantage for program or element termination if the combination has no effect or if the combination effect is not greater than one of the elements. If the combination is of an add-on therapy to a marketed agent such as an anti-amyloid MAB, the combination must perform better than the anti-amyloid MAB by itself for the novel therapy to warrant continued development. In the design and reporting of trials with factorial designs, the reasons for using the factorial design, the justification of the agents included, the main comparisons to be analyzed, and the anticipated interaction effects should be specified[65].

A trial of vascular cognitive impairment proposed a 2-by-2 factorial design of isosorbide mononitrate that augments the phosphodiesterase 5 (PDE5)-inhibitor pathway, and cilostazol, a PDE3 inhibitor that enhances the prostacyclin-cyclic adenosine monophosphate pathway. Both these pathways modulate endothelial function and combination therapy is hypothesized to improve cognition in patients with vascular dementia. These are repurposed agents approved for treatment of vascular diseases; have no known interactions; and have adverse event profiles that support their safe use in combination[66]. The design planned 100 patients per arm with feasibility and safety being the primary outcomes. Data on death, vascular events, and cognition are collected.

An adaptive trial design that modifies the factorial approach can be used to determine if the single agents have less activity than the combination. If the individual agents fail to show efficacy but the combination is efficacious, development of the individual agents can be suspended and development can concentrate on the combination treatment. This outcome can occur if the interaction of the contributing agents is synergistic rather than additive. If either agent performs like the combination, development of the combination therapy may be unnecessary. Adaptive designs may save time and require fewer participants to guide development decisions[12,67].

A "fast fail" strategy may be desirable in some circumstances. For novel combinations, the combination would be compared with placebo, possibly with biomarker readouts (Fig. 1). If there is no drug placebo difference, the program can be stopped or substantially reconsidered. An absence of effect of the combination suggests an absence of effect of either agent unless the agents are somehow antagonistic. If a drug-placebo difference is observed, further testing of A and B is warranted to determine if one or both are responsible for the observed efficacy. This approach was used for the development of COVID therapies, where accelerating testing of combinations allowed the greatest chance of discovering efficacy without waiting for the conclusion of monotherapy trials[68]. For add-on therapy, the" fast fail" approach would compare combination therapy to the standard of care (e.g., treatment with an anti-amyloid MAB only) (Fig. 2). If the novel agent shows no effect beyond that observed with the MAB, the program can be stopped or reconsidered (e.g., is the dose optimized). If the add-on is superior to the MAB-only arm, then further development of the novel agent is warranted.

Phase 2 decisions may depend primarily on the biomarker outcomes observed in both monotherapy and combination therapy trials. Knowing the biomarker outcome profile of each agent of a combination is the basis for interpreting the biomarker changes observed in the combination therapy setting. Assessment of clinical outcomes in Phase 2 may depend on effect size calculations, consistency across measures, directionality and magnitude of response without necessarily achieving a conventional threshold of statistical significance[69].

Determination of dosing of a combination builds on information

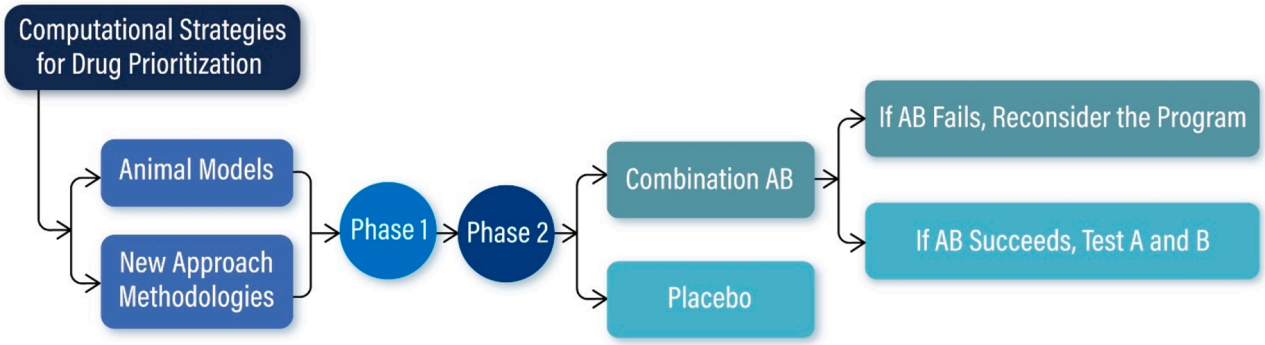

Fig. 1. "Fast fail" approach for novel combination with advancing of the novel agents only the novel combination performs better than placebo.

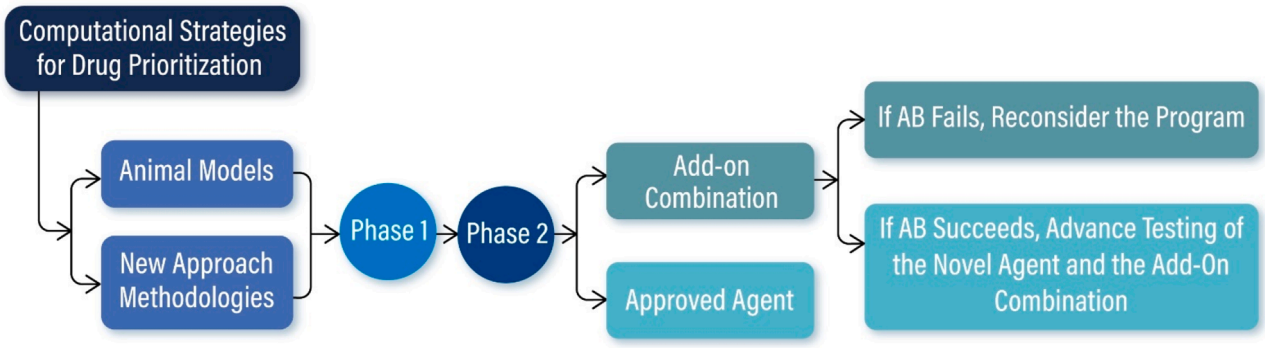

Fig. 2. "Fast fail" approach for add-on combination with advancing of the novel agent only if it succeeds in performing better than approved agent without the novel agent.

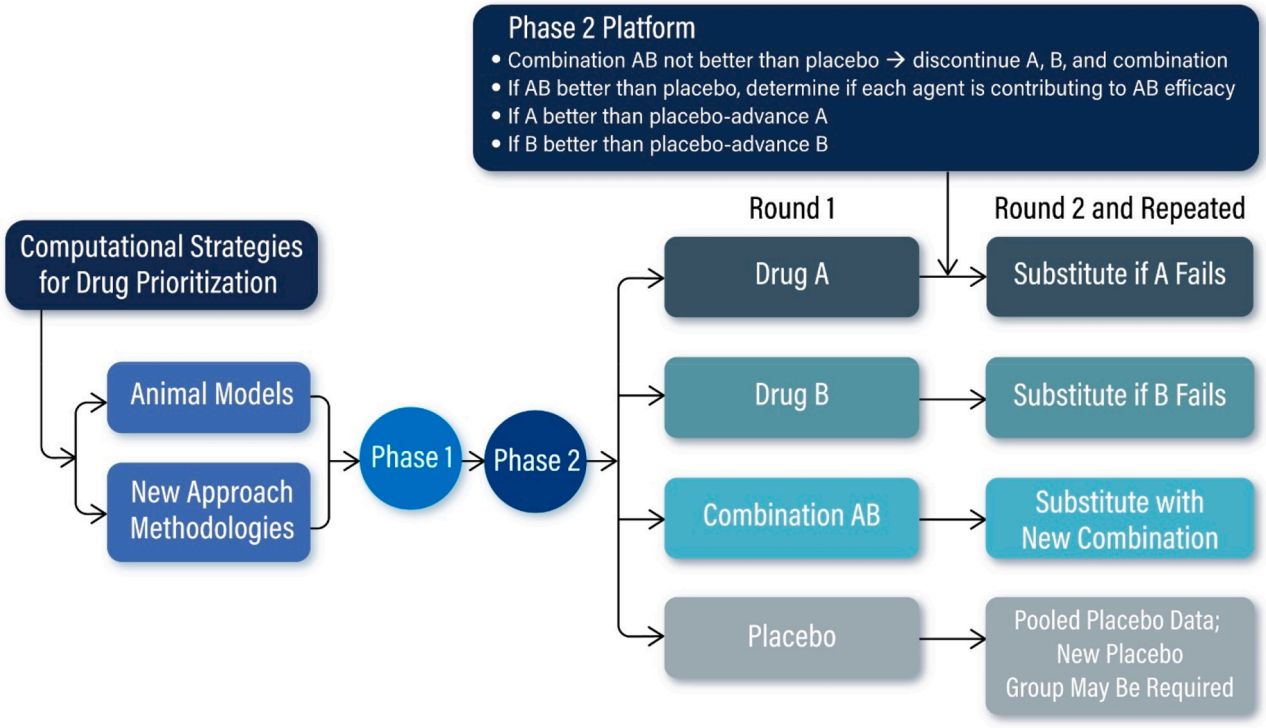

Fig. 3. Factorial 2 × 2 combination platform design with Bayesian analysis and progression to 2nd round agents and combinations if the first candidates and candidate combinations do not show efficacy.

derived in Phase 1 regarding escalating doses of each agent in the combination. Assessment of multiple dose combinations may be required to establish an optimal dose or doses for combination drug testing in Phase 3. Doses of combination treatments may be lower than those required for monotherapy of the individual agents if synergistic efficacy is demonstrated. Such combinations may have less toxicity than monotherapy alone.

3.4. Phase 3 of a combination therapy development program

Biomarkers have a key role in Phase 2 and may inform the decision to progress a compound to Phase 3. In Phase 3 programs, demonstration of clinical efficacy will be required for drug approval. Exceptions might include situations where biomarkers can inform regulatory decisions such as in prevention trials or in accelerated approval.

The design of Phase 3 clinical trials will depend on information derived from Phase 2 and the nature of any remaining questions regarding efficacy and safety of novel agents or the combination. If Phase 2 trials demonstrate the contribution of each novel agent or the contribution of a novel agent as an add-on to standard of care such as an anti-amyloid MAB, then Phase 3 may be a two-arm study comprised of a combination of the novel agent and the anti-amyloid MAB compared to the anti-amyloid MAB by itself. This design would establish the efficacy of the combination and of the contribution of the novel agent to the combination[12].

If substantial questions remain after Phase 2 regarding a novel combination, a 2-by-2 factorial design may be required[70] (Fig. 3). Adaptive modifications of the factorial design may be applicable. A three-arm design comparing drug A and drug B to the combination AB may be appropriate in some circumstances (Fig. 4). If the combination AB is superior to drug A, then drug B must be contributing, and if the combination AB is superior to drug B, then drug A must be contributing [12]. Other types of factorial designs such as a 2-by-2-by-2 where two dose levels of each agent are assessed or factorial designs allowing three interventions to be studied can be considered. Fractional and nested factorial designs can be used when they best meet the needs of the development program[71].

Other designs may be possible and will be negotiated with the FDA or other regulatory agencies prior to trial initiation[60].

3.5. Analytic and planning strategies for combination trials

There are analytic and planning challenges unique to combination therapies. For example, adverse events may now occur from two or more therapies included in the combination therapy, and this may increase attrition rates. Prediction of attrition and adjustment of sample size will be important preemptive strategies to preserve the power of analyses.

Drug interactions must be anticipated in combination trials. Combinations therapy therapies may show synergistic effects, additive effects, or antagonistic effects. At the non-clinical level (in vitro or in vivo) these can be experimentally characterized allowing simulations of human data and analytical planning for combination trials[72].

Clinical trial designs (discussed above), clinical observations collected in the trial, and biomarkers all contribute to the weight of evidence that will determine whether an agent should be progressed, stopped, or directed to trials where critical missing data can be generated. Pre-specification of decision rules based on the sponsor's model of AD and expected biomarker and clinical outcomes gives increased credibility to the conclusions drawn from the trial and the derived action plan. Bayesian adaptive designs may offer advantages in combination trials where there are uncertainties in terms of responsive population, dose, or best outcome. Adaptive designs require greater pre-specification but allow adjustment of key trial features based on data collected during the trial[73].

4. Platform trial designs for combination therapies

Platform trials are governed by a master protocol that allows for the evaluation of multiple therapies that enter the platform and may matriculate to further trials or be discontinued based on the trial data collected (Figures 3 and 4). Platform trials have operational efficiencies such as a standing network of participating sites, shared placebo data, and seamless progression for testing one agent or combination to another. Data on novel biomarkers and clinical outcomes across a variety of trials and types of interventions can be accrued. Trial learnings are incorporated into trial decisions as the trial proceeds. The flexibility of platform trials requires extensive pre-trial specification of trial operations. Analytic approaches and decision rules must be prospectively determined. Trial simulations may be used to explore the likely outcomes of trials using different types of decision rules[74]. The DIAN-TU and the Alzheimer Tau Platform are examples of applying the platform approach to the development of combination therapies[24,25].

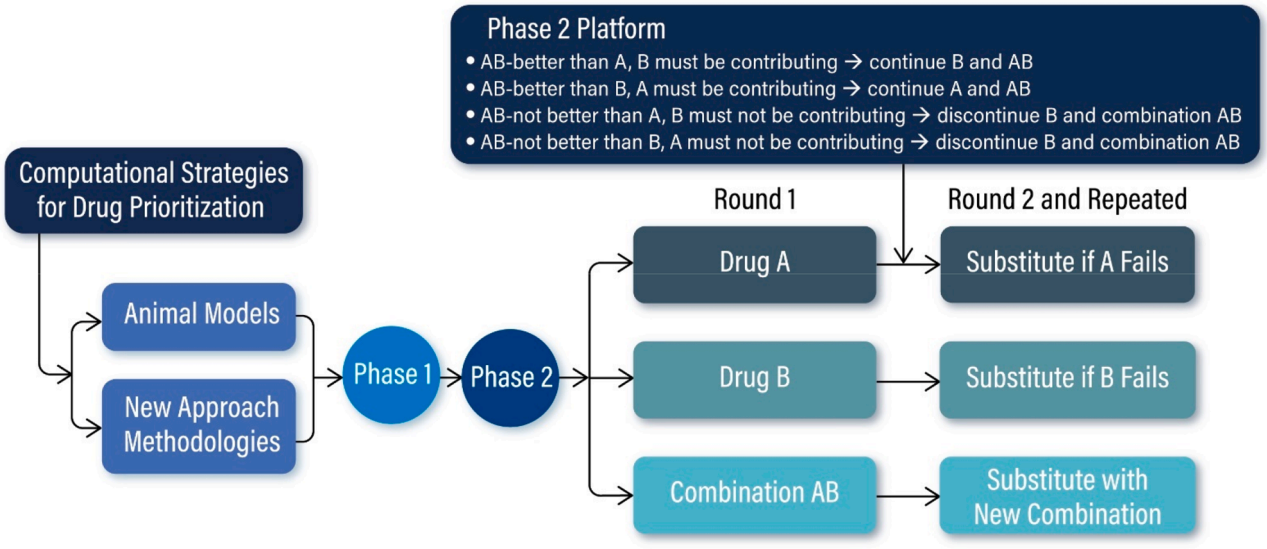

Fig. 4. Three arm combination therapy platform design comparing each drug to the comparison to determine if the comparison is superior to each drug alone and progression to substitute agents if the original candidates do not show efficacy.

5. Biomarkers in clinical trials of combination agents

Biomarkers guide clinical trial decision making and have become a key aspect of successful drug development[9,75]. The FDA-NIH Biomarker Work Group has defined the context of use for biomarkers in clinical trials[76]. The specified roles include diagnosis, risk determination, prognostic forecasting, pharmacodynamic response, monitoring, benefit or harm prediction, and safety. Table 2 shows each of the contexts of use and the role they may play in trials of combination therapies.

In AD clinical trials, diagnostic biomarkers detect or confirm the presence of AD. Confirmation of the presence of amyloid pathology with amyloid PET, CSF AD signature studies, or plasma p-tau 217 are used to establish the diagnosis of AD in both monotherapy trials and trials for combination treatments. Conduct of trials for treatments of AD, monotherapy or combination treatments, should confirm the diagnosis of AD as a requirement for trial participation.

Risk biomarkers may differ in monotherapy and combination therapy trials if one of the disease targets influences the risk for AD. For example, diabetes is a risk factor for AD and a combination containing a drug repurposed from the treatment of diabetes might perform differently in a population enriched for this risk state.

Prognostic biomarkers may assist in identifying populations that are more likely to decline during a trial, optimizing the opportunity to observe a drug-placebo difference. Higher levels of p-tau 217 are associated with a greater likelihood of progression to AD dementia in individuals with MCI due to AD[77].

Two types of pharmacodynamic response biomarkers are of value in AD clinical trials. Target engagement biomarkers measure the degree to which the drug interacts with the pharmacologic or mechanistic target. For example, anti-amyloid MABs are directed at fibrillar plaque amyloid detected by amyloid PET. Target engagement with reduction in plaque burden is reflected by diminished plaque burden revealed by this imaging biomarker. Target engagement biomarkers that are unique to each member of a combination therapy would be particularly valuable to establish the independent biological effects of the combination elements.

Disease impact pharmacodynamic biomarkers report on the degree to which the therapy changes the underlying biology of the disease. For example, removal of amyloid plaque is accompanied by changes in downstream biomarkers including p-tau 217, GFAP, and neurogranin[4,5,78]. The importance of these biomarker changes is supported by their relationship to slowing of the progressive decline of AD. In trials of combination therapies, it may be difficult to discern the independent impact of each agent on biomarkers if they have similar downstream effects. The impact of the combination on the timing, trajectory, or magnitude of response may be informative if these parameters differ from that observed in trials for each of the contributing agents of the combination.

There are few predictive biomarkers for AD clinical trials. The presence of the apolipoprotein E ε4 (*APOE4*) gene predicts an increased risk of ARIA. In studies of donanemab, high levels of neurofibrillary tangles observed on tau PET predicted a failure of response to the anti-amyloid MAB[4]. As more predictive biomarkers are discovered, they may have an increasingly important role in trials of combination therapies.

Monitoring biomarkers are collected serially to determine the effects of treatment. Plasma biomarkers lend themselves to this context of use. In AD trials of anti-amyloid MABs, serial measures of p-tau 217, p-tau 181, Aß 42/40, and GFAP have proven to be useful in monitoring the therapeutic response[5,23,78]. Serial measurement of any biomarker that is uniquely or disproportionately related to the impact of each agent in the combination will be helpful in determining the contribution of the component aspects of the combination therapy.

Safety biomarkers include MRI for the detection of ARIA in trials of anti-amyloid MABs as well as blood tests monitoring for drug induced liver injury (DILI), treatment-related cardiac irregularities, or other laboratory abnormalities[79]. MRI may play a key role in combination trials that include anti- amyloid MABs. Safety biomarkers may help understand adverse events associated with each element of the combination. ARIA occurring in patients on anti-amyloid MABs are most likely to be due to the MAB, but ARIA can occur spontaneously in patients with cerebral amyloid angiopathy (CAA) and rarely occurs in response to other types of treatment[80]. Similarly, monitoring liver function tests will be helpful, particularly if liver abnormalities have been observed with one of the agents in preparatory monotherapy trials.

Biomarker-based analytic and trial design strategies can be used to answer questions central to drug development. Populations can be stratified based on biomarkers to allow pre-specified analyses of biomarker subgroups in a trial (e.g., *APOE4* carriers vs noncarriers; those with higher levels of inflammatory markers at baseline compared to those with lower levels; those with higher vs lower levels of tau as demonstrated on tau PET at baseline). Prognostic factors may be used to enrich populations to ensure decline in the placebo group (e.g., p-tau 217, tau PET)[81,82]. Biomarkers might be used for interim analyses of early-stage trials to assess target engagement, adjust sample sizes, or declare futility if no or little biomarker change confidently predicts an absence of potential clinical benefit. Pharmacokinetic/pharmacodynamic modeling of biomarkers may inform understanding of treatment effects on biomarkers and relationships among biomarkers in combination treatments trials[83].

Table 2
Context of use of biomarkers in combination and add-on trials.

Context of Use	Combination and Add-on Therapy Trials
Diagnosis	Diagnostic standards will be similar or identical for monotherapy and combination therapy trials
Risk	Might differ from monotherapy trials if the add-on agent or novel combination has potential impact based on the specific indicator of risk (e.g., the presence of diabetes in an AD population)
Prognosis	Prognostic biomarkers might differ in combination trials from monotherapy trials if the members of the combination have differential impacts on populations on different disease trajectories
Pharmacodynamic: target engagement	Target engagement biomarkers would be of use for all members of a combination therapy to provide insight into the pharmacological impact of each agent
Pharmacodynamic: disease impact	Biomarkers of disease impact may differ depending on the targeted processes of the members of the combination
Monitoring	Monitoring biomarkers may differ in combination trials and monotherapy trials if a biomarker of disease impact differs for the combination therapy compared to immunotherapy approach
Predictive	Predictive biomarkers of efficacy may differ when combination therapies address multiple biologies compared to a single biology addressed by monotherapy. Predictive safety biomarkers may differ for a combination with multiple components compared to monotherapy
Safety	Safety biomarkers may differ for monotherapies and combination therapies. Components of combination therapies might have corresponding safety liabilities involving liver dysfunction, ARIA, etc.

APOE4 - apolipoprotein E ε 4; ARIA - amyloid related imaging abnormalities.

6. Choosing agents for combination therapies

It is a challenge to decide how best to construct a combination therapy whether two novel interventions are being considered or an add-on therapy with a novel agent and an anti-amyloid MAB is planned. AD is a complex disorder with core features including amyloid and tau

protein abnormalities, non-specific pathophysiological changes that accompany the core features including inflammation and neurodegeneration, and co-pathologies such as alpha-synuclein and TDP-43 [3]. In addition, mitochondrial abnormalities, oxidation, synaptic plasticity alterations, epigenetic changes, and lipid and lipoprotein abnormalities are present in AD and may comprise therapeutic targets[84]. Choosing among these targets for development of combination therapies depends on the body of information justifying the target, the availability of biomarkers to monitor a therapeutic response, and the characteristics and developmental stage of candidate agents for the potential use in combination therapies.

Computational strategies are emerging that may assist in identifying the highest priority agents for use in the combination therapy setting. Network medicine approaches are becoming increasingly sophisticated and incorporate an expanding universe of informative data sets. Genome wide association studies (GWAS) and "omic" databases increasingly inform disease network mapping. Known drug networks can be explored to determine their proximity to disease networks and the relative likelihood of an impact on disease processes[85]. Candidate therapies can be assessed in animal models, organoids, or IPS cells to validate their biological effects. In the case of repurposed drugs, electronic medical records can be studied to determine if drug exposure resulted in decreased disease incidence. Clinical trial emulation can be conducted on electronic medical record data to determine if virtual trial data support efficacy of an agent or a combination[62]. The convergence of multiple types of information using computational strategies would support prioritizing some agents over others[86]. These strategies have been used to predict the likely efficacy and risk of side effects of combination therapies for AD[87,88]. These approaches have not yet predicted a successful AD therapy, but the advances in computational approaches suggest that they will become a valuable part of combination treatment development.

7. Discussion and conclusion

Combination add-on therapies with anti-amyloid MABs are being conducted in DIAN-TU and the Alzheimer Tau Platform and more add-on combinations are anticipated[24,25]. In some cases, anti-amyloid MABs will be allowed in trials but not required, creating subpopulations on combination therapies. In others, anti-amyloid MABs may be the standard of care to which novel interventions are added. A wide array of combinations of therapeutic types are being studied including combinations of drugs, MABs and other biological therapies, devices, gene therapies, cell therapies, and lifestyle interventions. Progress in understanding the neurobiology of AD facilitates more cogent choice of elements of a combination therapy, and emerging computational strategies may play an increasingly important role in prioritizing candidates for combinations.

While the logic of combination therapies is compelling, there are substantial hurdles to combination drug development[89] . Two novel agents may not be available in the same company or may be at different phases of development, making testing in a single trial difficult. A consensus strategy for prioritizing compounds or pathways that are most promising to address in combination trials has not been achieved. Clinical trials of combination therapies are complex and may require unrealistically large number of numbers of patients to demonstrate differences between combination therapies and monotherapies particularly if one of the agents in the combination is accounting for most of the therapeutic response. Repurposed agents may lend themselves to combination trials but lack of resources for late-stage development limits the likelihood that such treatments will become approved therapies. The "right" population may differ for the agents in the combination diminishing the effectiveness of the combination in trials involving single populations of the AD continuum are conducted.

A variety of clinical trial designs with two, three, and four arms are feasible depending on the type of information required. It is important for sponsors to thoroughly characterize the individual agents of a planned combination prior to assessing the agents together in a combination approach or add-on trial. Interpretation of clinical effects, biomarker effects, and adverse events depends on thorough understanding of each agent in the combination.

Creating a trial infrastructure to support combination trials is needed. Platform trials have been used to develop combination therapies in oncology and lessons from this experience can be applied to platform trials in AD and NDDs. DIAN-TU and the Alzheimer Tau Platform represent progress in developing platform trials for add-on drug combinations[24,25].

Treatment with MABs requires substantial practitioner and health care resources. Many countries currently cannot divert funding from other high priority areas to these emerging therapies. Add-on therapies to MABs may make regimens more complex and further decrease accessibility. Combination therapies consisting of agents that are easier to administer may improve global access to effective therapies.

The new therapeutic era introduced by anti-amyloid MABs creates new opportunities and new challenges. Add-on therapy to MABs may further slow disease decline and produce greater patient benefit. The landscape of anti-amyloid MAB use is evolving rapidly. Progression in understanding of AD pathophysiology requires a therapeutic response that reflects the complexity of the illness. New therapies are emerging, and new combinations will be identified. The goal of preventing, arresting, or substantially slowing the progression of AD will depend on resolving the issues involved in developing combination therapies. Precision medicine addressing AD and co-pathologies will depend on combinations of biomarkers guiding a corresponding regimen of therapies. The implementation of precision medicine requires understanding the risk and resilience factors of individual patients and choosing combinations of medicines with low likelihood of interactions and harm and high likelihood of benefit.

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CRediT authorship contribution statement

Jeffrey L Cummings: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Aaron H Burstein:** Conceptualization, Writing – review & editing. **Howard Fillit:** Conceptualization, Writing – review & editing.

Declaration of competing interest

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

Jeffrey L Cummings reports a relationship with Acadia Pharmaceuticals Inc that includes: consulting or advisory. Jeffrey L Cummings reports a relationship with Acumen Pharmaceuticals Inc that includes: consulting or advisory. Jeffrey L Cummings reports a relationship with ALZpath Inc that includes: consulting or advisory. Jeffrey L Cummings reports a relationship with Annovis Bio Inc that includes: consulting or advisory. Jeffrey L Cummings reports a relationship with Artery Therapeutics Inc that includes: consulting or advisory. Jeffrey L Cummings reports a relationship with Axsome Therapeutics Inc that includes: consulting or advisory. Jeffrey L Cummings reports a relationship with Biogen Inc that includes: consulting or advisory. Jeffrey L Cummings reports a relationship with Biohaven Ltd that includes: consulting or

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Special Article

Add-on combination therapy with monoclonal antibodies: Implications for drug development

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Alzheimer's disease

ABSTRACT

Three anti-amyloid monoclonal antibodies (MABs) including aducanumab, lecanemab, and donanemab have been approved by the FDA and lecanemab and donanemab are available in the US market and a variety of other national markets. The increasing use of anti-amyloid MABs to treat early AD will require that development of novel agents occur as add-on treatment to MABs. There is limited experience with add-on therapy to anti-amyloid agents. In most cases, it is prudent to initiate novel agents after at least six-months exposure to the MAB at the highest dose. Agents with extensive data on pharmacokinetics and pharmacodynamics and well-known safety may employ alternative approaches. Anti-amyloid MABs have different mechanisms of action, titration, and side effect profiles suggesting that add-on trials include only one type of MAB if possible. Demonstration of clinical benefit with add-on therapy will require showing additional slowing beyond that provided by the anti-amyloid MAB. Anti-amyloid therapies have profound effects on biomarkers including amyloid positron emission tomography and plasma p-tau and plasma GFAP measures. Definition of the biomarker profile of a novel agent prior to initiation of add-on therapies, inclusion of target engagement biomarkers specific to the novel intervention, assessment of biomarkers not known to be affected by anti-amyloid MABs, and interrogation of the magnitude, timing, and trajectory of biomarker change in the add-on context compared to monotherapy with MABs will provide insight into the biological impact of the novel therapy on AD. Patient convenience in terms of formulation and timing of add-on therapies will be important to successful clinical implementation. Add-on therapies are an important step in addressing the complexity of AD and optimizing patient outcomes.

1. Introduction

Anti-amyloid monoclonal antibodies (MABs) are the first approved disease-targeted therapies (DTTs) for Alzheimer's disease (AD). They have shown efficacy in early AD (mild cognitive impairment [MCI] and mild dementia due to AD). Aducanumab (Aduhelm®), lecanemab (Leqembi®), and donanemab (Kisunla®) have been approved, and lecanemab and donanemab are currently available on the market in the United States and are approved or being considered for approval in additional world regions [1,2]. MABs markedly reduce amyloid beta protein (Aβ) plaques and slow progression of clinical symptoms of early AD by approximately 30 %. Participants in clinical trials of novel agents may be receiving treatment with anti-amyloid MABs, and the novel agent being assessed in the trial will be an add-on therapy [3]. How existing anti-amyloid MAB therapy may affect clinical outcomes, biomarkers, and adverse events in clinical trials of novel agents is a new area of clinical trial and drug development planning. Here we describe options for the design and conduct of clinical trials of add-on therapies to MABs for treatment of AD.

2. Definitions of combination therapies

We address a specific type of combination therapy in which one or more novel agents is added on to an existing DTT, specifically an anti-amyloid MAB. Participants in these trials have begun therapy with an anti-amyloid MAB and then enter a clinical trial for a novel agent or may be treatment naïve and are begun on a MAB prior to initiating treating with the novel add-on therapy. Other types of combination therapies include development of two or more novel agents that are administered simultaneously or the development of combination products involving

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combinations of drug, device, and biological agent. Subcutaneous administration of an anti-amyloid MAB with an autoinjector is an example of a combination product as defined by the Food and Drug Administration (FDA).

There are substantial challenges in conducting and analyzing clinical trials of novel agents that include participants on anti-amyloid MABs. When to start the novel treatment in relation to the MAB therapy, whether to specify which MAB(s) is(are) allowable, whether to require a specific level of treatment-related amyloid clearance (TRAC) among trial participants, how to accurately attribute adverse events to the MAB or to the add-on therapy, how to interpret the effects of novel therapies on biomarkers in patients on anti- amyloid MABs and exhibiting substantial biomarker changes at baseline, how to choose novel agents to add-on to MAB therapies, and how to analyze outcomes of add-on trials represent important challenges that must be resolved in planning comprehensive drug development programs allowing participants on MABs. We address the main issues below.

3. Anti-amyloid monoclonal antibodies

3.1. Lecanemab and donanemab

Appropriate use recommendations (AURs) are available for lecanemab and donanemab [4,5]. Appropriate candidates for anti-amyloid MAB therapy are those with early AD manifesting Mini-Mental State Examination (MMSE) scores of 20 or higher. Patients must have confirmed Aβ pathology by amyloid positron emission tomography (PET), cerebrospinal fluid (CSF) findings consistent with AD, or highly accurate plasma blood biomarkers such as phosphorylated tau 217 (p-tau 217) in the abnormal range. A baseline magnetic resonance imaging (MRI) scan must show no more than 4 microhemorrhages and should not demonstrate extensive white matter changes. Patients should have genetic testing for the apolipoprotein E ε4 (*APOE4*) genotype since the risk of amyloid related imaging abnormalities (ARIA) is higher in *APOE4* gene carriers, and there is a gene dose effect with the highest risk among *APOE4* homozygotes (discussed in more detail below). Patients with a history of seizures or autoimmune disorders or who are receiving anticoagulant therapy are not appropriate candidates for treatment. AURs are derived from clinical trials and expert opinion and do not supersede clinician judgement for individual cases.

The AURs for anti-amyloid MABs apply to all add-on trials with these agents. Trials of drugs being developed for early AD, for example, may include a substantial number of patients on anti-amyloid MABs since these agents are approved only for patients with early AD at the time of treatment initiation. Novel agents being developed for treatment of mild to moderate AD would be expected to have fewer participants eligible for add-on therapy since initiating MAB therapies in patients with moderate AD would be an inappropriate use of these agents. All patients receiving anti-amyloid MAB therapy will have had a biologically confirmed diagnosis of AD at the time the MAB treatment was initiated. After treatment they may no longer meet amyloid-related criteria for the diagnosis of AD. Repeat of diagnostic studies would not be required unless the novel agent is expected to affect Aβ plaques or CSF or plasma Aβ-related measures and changes from baseline are possible outcomes of therapy. Trials of novel agents in trials allowing participants on MAB therapies will be studying patients who at the time of beginning MAB treatment initiation had 4 or fewer microhemorrhages in the brain, a low burden of white matter pathology, no history of seizures or immune system disturbances, and were not on anticoagulants. Candidates for anti-amyloid MAB treatments must be MRI-eligible since MRI is required to define the baseline the presence of microhemorrhages and to monitor for ARIA. Patients with MRI incompatible pacemakers, claustrophobia, or other reasons for not being able to have an MRI will be excluded from these add-on trials since they would have been ineligible for MAB therapy. These treatment population restrictions will limit the generalizability of conclusions that can be drawn from the trial regarding the effect of the novel agent.

The therapeutic targets, administration frequency, and titration requirements differ for lecanemab and donanemab (Table 1). Lecanemab targets Aβ protofibrils and plaques. The agent is administered intravenously every two weeks; infusion frequency may be decreased to monthly after 18 months of treatment. Lecanemab does not require titration. Therapy is continued until the patient, family, and clinician conclude that continuing therapy is of no benefit. A subcutaneous version of lecanemab is being studied.

Donanemab targets pyroglutamate Aβ found only in fibrillar Aβ plaques. It is administered intravenously monthly for 18 months or until an amyloid PET demonstrates the absence of plaques in the brain. Donanemab is titrated in 2 or 4 dosing steps; the 4-step titration schedule may be associated with a lower frequency of ARIA.

Not all patients receiving anti-amyloid MABs have complete TRAC. Patients included in add-on trials will include a combination of full TRAC and partial TRAC individuals unless the trial requires dmonstration of an absence of detectable Aβ plaques.

ARIA of the effusion type (ARIA-E) or of the hemorrhagic type (ARIA-H) represent the principal side effects associated with anti-amyloid MABs. ARIA is usually asymptomatic but may produce symptoms such as confusion or gait disturbance and can be severe enough to produce status epilepticus or death; treatment candidates must understand the risks associated with MAB treatment. Serial MRIs are collected in the

Table 1
Key features in the active treatment arms of the lecanemab an donanemab observed in Phase 3 trials. The agents have not been directly compared in clinical trials and comparative observations are preliminary.

Drug or Trial Feature	Lecanemab	Donanemab
Target	Protofibrils and plaques	Pyroglutamate amyloid in Aβ plagues
Infusion schedule	Twice monthly for 18 months; monthly thereafter	Monthly
Stop treatment with demonstrated plaque removal	No	Can be considered; treatment was stopped following plaque removal in clinical trials
Titration	None required	2 step titration: 700 mg x3 then 1400 mg on infusion 4 and thereafter 4 step titration: 350 mg x1; 700 mg x1; 1050 mg x1; 1400 mg on infusion 4 and thereafter
Primary outcome: percent reduction in rate of decline	2CDR-SB: 7 % slowing	iADRS: 35.1 % slowing (low/medium tau group)
Secondary outcome/ ADAS-cog: percent reduction in rate of decline	26 % slowing	32.4 % in the low/medium tau group
Secondary outcome/ ADCS-ADL percent reduction in rate of decline	36 % slowing	39.9 % in the low/medium tau group
ARIA - E	12.6 %	24 %
Symptomatic ARIA-E	2.8 %	6.1 %
ARIA-E: noncarriers	1.4 %	15.7 %
ARIA-E: APOE4 heterozygotes	1.7 %	22.8 %
ARIA-E: APOE4 homozygotes	9.2 %	40.6 %
ARIA-H	17.3 %	19.7 %
Percent with infusion reactions	26.4 %	8.7 %

Aβ - amyloid-beta protein; ADAS-cog - Alzheimer's Disease Assessment Scale - cognitive subscale; ADCS-MCI-ADL - Alzheimer's Disease Cooperative Study Mild Cognitive Impairment Activities of Daily Living scale; ARIA-E - amyloid related imaging abnormalities - edema type; ARIA-H - amyloid related imaging abnormalities - hemorrhagic type; CDR-SB - Clinical Dementia Rating Sum of Boxes; iADRS - integrated Alzheimer's Disease Rating Scale

initial phases of anti-amyloid MAB therapy to detect asymptomatic ARIA and guide management. Treatment with MABs is discontinued if patients have symptomatic ARIA, more than 2 episode of ARIA, or have severe ARIA as revealed by MRI. Treatment is paused if ARIA is moderate and may be resumed if ARIA-E resolves or ARIA-H stabilizes. Treatment may continue in patients with mild ARIA (observed on MRI) who are asymptomatic [4,5]. The initiation phase of the MAB should be completed before therapy with a novel agent is begun.

In the Phase 3 trial, lecanemab was associated with ARIA-E in 12.6 % of participants receiving active therapy [2]. Symptoms of ARIA-E were apparent in 2.8 % of participants. ARIA- E was more frequent in *APOE4* homozygotes (9.2 %) compared to heterozygotes (1.7 %) or noncarriers (1.4 %). ARIA-H occurred in 17.3 % of participants and was symptomatic in 0.7 %. Approximately half of the cases of ARIA-H occurred in participants with ARIA-E. Seventy-one percent of ARIA events occurred within the first three months of therapy, and 81 % resolved within four months after detection. Infusion reactions occurred in 26.4 % of participants treated with lecanemab.

In the Phase 3 trial of donanemab, ARIA-E occurred in 24 % of participants receiving active therapy and ARIA-H occurred in 19.7 % [1]. ARIA-E was symptomatic in 6.1 % of participants. ARIA-E occurred in 15.7 % of *APOE4* noncarriers, 22.8 % of *APOE4* heterozygotes, and 40.6 %of *APOE4* homozygotes. Most ARIA (57.9 %) occurred within the first three months of treatment. Infusion reactions occurred in 8.7 % of individuals receiving donanemab.

3.2. Anti-amyloid monoclonal antibodies in development

Lecanemab and donanemab or currently available in the US and several other countries. Other anti-amyloid MABs are in clinical trials and could progress to approval include MABs in Phase 3 (remternetug and tertomidine) and MABs in Phase 2 (ABBV-916, sabirnetug, SHR-1707, and trontinemab). Add-on trials including patients on any of these agents can be anticipated.

4. Add-on clinical trials with anti-amyloid antibodies

4.1. Add-on treatment with existing approved treatments

Cholinesterase inhibitors (donepezil, galantamine, rivastigmine) are approved for mild and moderate AD dementia, and donepezil and rivastigmine are approved for severe AD dementia. Memantine is approved for moderate to severe AD dementia [6]. Patients on these drugs have been allowed in clinical trials of anti-amyloid MABs as the standard of care for patients with AD. In the Phase 3 lecanemab clinical trial, 52 % of patients on active therapy were receiving treatment with standard of care (some combination of cholinesterase inhibitors and memantine) [2], and in the Phase 3 trial of donanemab, 56.5 % of patients in the low/medium tau group and 60.6 % of patients on the combined tau group (low/medium tau and high tau) were on standard of care with approved agents [1]. These observations indicate that approximately 50 % of the participants in the anti-amyloid MAB trials were receiving add-on therapy of the MAB to standard of care. Pre-specified sub-analyses are typically conducted to determine if the existence of standard of care influences the clinical outcomes. Development of novel agents as add-on therapies to anti-amyloid MABs are anticipated to include participants on standard of care therapies including cholinesterase inhibitors or memantine.

4.2. Rationale for development of new add-on therapies

There are several reasons to pursue add-on trials with anti-amyloid MABs. AD is a complex disorder with Aβ abnormalities, tau protein aggregation, neurodegeneration, inflammation, oxidative and metabolic abnormalities, synaptic dysfunction, and transmitter deficits, as well as co-pathologies in some patients such as alpha-synuclein and TAR DNA binding protein 43 (TDP-43)(7). Anti-amyloid MABs address one aspect of this complex pathobiology, and achieving a therapeutic response of greater magnitude may involve add-on therapies that have additive or synergistic effects beyond those of the anti-amyloid therapy alone.

Anti-amyloid MABs produce an approximately 30 % slowing of disease progression. The goal of caring for patients with AD is to further slow, stop, or reverse progression; add-on therapies are required to achieve these goals [8,9].

Combination therapies might address safety issues of MABs. ARIA-E and ARIA-H follow interruption of the blood brain barrier, and the likelihood of ARIA may be enhanced by the presence of vascular inflammation [10]. Add-on therapies that reduce peripheral inflammation or enhance blood brain barrier integrity may reduce ARIA and improve the safety of anti-amyloid MAB therapy.

Since many early AD patients may be on anti-amyloid MABs, establishing the safety and efficacy of add-on therapy is important to assure clinicians that, if the test agent is approved, it can be employed in their patients receiving MAB treatment.

4.3. Rationale for specific combinations of treatment in add-on trials

A variety of types of add-on therapies might be considered for patients receiving anti-amyloid MABs. For example, tau abnormalities are another core AD pathology and could be targeted in an add-on trial [7]. Tau therapies could complement the effects of the Aβ-directed therapies, and this hypothesis is currently being tested with the anti-tau agent, E2814, combined with lecanemab in participants with dominantly inherited Alzheimer's disease (DIAD) in the Dominantly Inherited Alzheimer Network Trial Unit (DIAN-TU).

Addressing pathophysiological changes that occur in AD including inflammation and neurodegeneration comprise potential therapeutic targets. Co-pathologies such as vascular changes, alpha-synuclein aggregates, and TDP-43 aggregation when shown to be present by emerging biomarkers could be targeted in patients who harbor these complex multi-protein combinations.

How to choose the best agent or combination of agents to add to anti-amyloid MAB therapy is a vexing challenge. Predictive efficacy tools are lacking. Computational strategies are a promising means of identifying drugs whose effects engage the AD pathological network and would complement the known effects of anti-amyloid MABs [11,12].

4.4. Timing of add-on therapy in clinical trials of novel agents

An important concern when considering add-on therapy to an anti-amyloid MAB is the occurrence of ARIA and its possible misattribution to the experimental agent. To avoid this, initiation of the test agent should occur after the period when most ARIA occurs with MAB treatment. ARIA events are observed relatively soon after initiation of anti-amyloid MAB treatment. Approximately 70 % of observed ARIA occurred within the first three months of treatment with lecanemab, and 60 % of documented ARIA occurred within the first three months of treatment with donanemab using the 2-step titration schedule.

No specific guidelines or studies have emerged regarding when to initiate treatment with a novel agent in the add-on setting. A prudent approach is to wait six months after initiation of the highest dose of the anti-amyloid MAB before introducing the novel agent. There is no dose titration with lecanemab, and initiation of the test agent could begin six months after initiation of lecanemab treatment. In the case of donanemab, a six-month observation period would suggest initiating treatment six months after initiation of treatment with the highest dose. Donanemab infusions occur at baseline and monthly thereafter, with the highest dose beginning with the 4th (highest) dose at the end of month 3.

In most cases, initiation of treatment with an anti-amyloid MAB after introduction of the novel agent in a trial should be avoided since the occurrence of ARIA in such patients could not automatically be attributed to the anti-amyloid MAB. Triggering Receptor Expressed on

Myeloid cells 2 (TREM)2 agents, for example, produce ARIA, indicating that ARIA is not unique to anti-amyloid MABs [13].

In unique instances when the scientific rationale and hypothesis for the pharmacologic effect and safety of the combination supports doing so, the novel therapy might be initiated prior to the start of the MAB (e.g., a study in an asymptomatic population where starting the novel therapy prior to start of MAB allows capture of data on the novel agent prior to co-administration with a MAB as is done in the DIAN-TU trial design). Another exception to delaying add-on of a novel agent for six months beyond the initiation of maximal therapy of the MAB are trial designs in which agents designed to reduce ARIA may be administered simultaneously with or prior to the anti-amyloid MAB with the intent of reducing this important side effect encountered with anti-amyloid MAB therapy. Anti-inflammatory agents may be candidates for this combination approach given the apparent relationships among vascular amyloidosis, inflammation, and ARIA risk [10].

4.5. Prespecification of the type of allowable MAB therapy in clinical trials

Sponsors will determine if they allow participants on any of the available anti-amyloid MABs or if a specific MAB will be required. The available MABs have different biological targets, different titration schedules, and different ARIA and infusion reaction liabilities (Table 1). Consideration of these aspects will influence whether sponsors allow participation of individuals on any MAB or will pre-specify the specific MAB population to be allowed. When randomizing treatment naive patients, sponsors could specify and provide a MAB and then add a novel therapy. Patients entering trials on MABs would continue MAB therapy if the agent is lecanemab and could have treatment stopped when amyloid plaque levels are sufficiently reduced if the agent is donanemab

Recruitment will be facilitated by allowing participants on any available MAB, however, trial operations and interpretation may be complicated by including patients on a variety of MABs. If the mechanism of action of the test agent interacts with the target of one of the MABs (e.g., protofibrils for lecanemab or pyroglutamate Aβ for donanemab) limitation of trial participants to one of the MABs may be desirable to facilitate understanding the biological impact of the novel agent. Glutaminyl cyclase inhibitors, for example, target pyroglutamate Aβ production and could interact with the mechanism of action of donanemab [14]. In allowing any available MAB, consideration should be given to management of patients who may clear amyloid during the study and would otherwise be candidates for discontinuation of the MAB (i.e., if receiving donanemab). Until additional data are available regarding the course of decline following discontinuation are available, an approach to minimizing variability in response over time favors standardizing the MAB and continuinh dosing during the double blind period of treatment with the novel agent. This may be particularly important for Phase 2 studies with small sample sizes.

4.6. Expanding the use of MABs in add-on trials

MAB add-on trials might provide the opportunity to extend the populations for which anti-amyloid MABs are indicated. Antibody therapies are currently indicated for patients with MCI due to AD or mild AD dementia. Expanded indications for use of MABS are currently being explored in trials of cognitively normal preclinical AD populations. Combination therapies in these studies could extend the period of normal cognitive function. Anti-amyloid MAB treatments in combination with other drugs could be explored in amyloid bearing conditions such as dementia with Lewy bodies, Down syndrome, Parkinson's disease dementia with concomitant amyloid plaques, and vascular dementia with concomitant AD pathology. These trials would represent new or expanded indication for MABs, and combination strategies may differ from those developed for early AD.

4.7. Clinical development plans for add-on therapies

Given the presence of anti-amyloid MABs in the market, the likely increase in the number of anti- amyloid MABs available, and the increasing treatment of early AD patients with anti-amyloid MAB therapy, clinical development plans of new therapies for AD should consider planning for add-on therapy as one aspect of the development program. Consideration should be given to the potential for safety issues following administration of novel treatments to participants on an anti-amyloid MAB. Non-clinical safety studies may be required to study these questions. In the absence of such concern, non-clinical studies may not be warranted.

4.8. Design of add-on trials

Several types of add-on trial designs for Phase 2 and 3 studies

Table 2
Clinical trial designs involving add-on strategies.

Clinical Trial Design	Information to be Derived
All participants are treated with an anti-amyloid MAB at a stable dose for a specific period and continue dosing for the duration of the trial, participants are randomized to: Arm 1: novel agent with MAB as background Arm 2: placebo with MAB as background	Sequential add-on design; novel therapy is introduced after ARIA risk has declined; allows safety and efficacy comparison of the add-on therapy (MAB + novel agent to the anti-amyloid MAB treatment (MAB + placebo)
Arm 1: novel agent allowing participants to be on anti-amyloid MABs Arm 2: placebo	Safety of the add-on therapy combination
Arm 1: novel agent allowing participants to be on anti-amyloid MABs Arm 2: novel agent alone (i.e., excluding participants on anti-amyloid MABs)	Safety of novel agent with and without add-on of anti-amyloid MAB
Arm 1: Combination treatment with novel agent requiring participants to be on anti-amyloid MABs Arm 2: Monotherapy of novel agent excluding participants on anti-amyloid MABs	Safety and efficacy of novel agent with and without add-on of anti-amyloid MAB
Arm 1: Combination treatment with novel agent requiring participants to be on anti-amyloid MABs Arm 2: novel agent alone (i.e., excluding participants on anti-amyloid MABs) Arm 3: Placebo	Frequentist design: Safety and efficacy of novel agent with and without add on anti-amyloid MABs; arms 1 and 2 can be compared to placebo (arm 3)
Arm 1: Combination treatment with novel agent requiring participants to be on anti-amyloid MABs Arm 2: Monotherapy of novel agent excluding participants on anti-amyloid MABs Arm 3: Placebo	Bayesian adaptive design: response-adaptive randomization allows adjustment of randomization probabilities to favor treatment arms demonstrating better efficacy or more favorable risk benefit profiles
Arm 1: Combination treatment with novel agent requiring participants to be on anti-amyloid MABs Arm 2: Monotherapy of novel agent excluding participants on anti-amyloid MABs Arm 3: Monotherapy of anti-amyloid MAB	Each agent (arms 1 and 2) is compared to combination (arm 3); if arm 3 exceeds arm 1, arm 2 must be contributing to efficacy; if arm 3 exceeds arm 2, arm 1 must be contributing to efficacy
Arm 1: Combination treatment with novel agent and anti-amyloid MABs Arm 2: novel agent along Arm 3: anti-amyloid MAB alone Arm 4: Placebo (control)	2 × 2 factorial design; each agent and the add-on combination are compared to placebo

MABs – monoclonal antibody; note: in all scenarios it is anticipated that trial design will require stable background therapy symptomatic medications (i.e., acetylcholinesterase inhibitors, memantine, unless contraindicated or not tolerated),

involving anti-amyloid MABs can be envisioned (Table 2). The specific design chosen will depend on the phase of development, objective of the study, data required to advance the treatment to the next phase or milestone, and logistical, operational, and financial considerations.

There are few precedents in AD drug development for establishing efficacy of add-on therapies. In the memantine development program, the efficacy of monotherapy was established in one trial and the efficacy of memantine in participants receiving donepezil was established in another [15]. In the add-on trial, all patients received donepezil and were then randomized to receive memantine or placebo; no placebo only arm was included [16]. Demonstration of efficacy in patients receiving donepezil suggested that combination therapy of the two agents was superior to monotherapy with donepezil alone. This strategy was also used in trials of aducanumab, lecanemab, and donanemab where standard of care was allowed and participants were randomized to the anti-amyloid MAB or placebo on top of stable symptom targeted therapies. A similar strategy might be followed for demonstrating the efficacy of a novel agent in patients receiving therapy with an anti-amyloid MAB. For registration trials, proposed study designs should be reviewed with regulatory authorities for feedback on appropriateness to support a proposed indication and product labeling.

Phase 1 trials will focus on establishing the safety and pharmacokinetic profile of the novel agent. At this stage of development, it is unlikely that add-on therapy designs will be employed given the importance of understanding the safety and pharmacokinetics of the novel agent before advancing into add-on trials. Biomarker data can be collected in the absence of anti-amyloid MAB effects; these data are critical to the interpretation of later add-on trials. If there are concerns regarding the potential for pharmacokinetic or pharmacodynamic interactions, with possible safety concerns, a Phase 1b add-on study in the target population may be required.

Combining novel therapies with MABs may offer the best opportunity for additive or synergistic disease slowing. The most efficient design at this stage may be the requirement that all subjects enrolled have been on stable treatment (for a least 6 months of the highest dose) with an anti-amyloid MAB followed by randomization to the novel agent (1 or more doses) or placebo. At this stage, trial emphasis is on safety and tolerability, evaluation of target engagement, and pharmacodynamic effect / biomarker changes for the combination vs MAB alone, while assessing qualitative evidence for directional change on cognitive measures. In these circumstances, the number of participants on anti-amyloid MABs would be small and analyses would be insufficiently powered to allow conclusions regarding enhanced clinical efficacy as an add-on therapy to the anti-amyloid MAB. Study of the directional outcomes of patients with add-on treatment versus monotherapy, the consistency of add-on versus monotherapy differences across outcome measures, the trajectory of monotherapy versus add-on treatment groups, and the effects on biomarkers of the two groups might provide preliminary information on possible additional efficacy of the add-on approach. Data generated from such trials inform the design of larger Phase 2b/3 trials required to establish the added benefit of combination therapy. Acknowledging the potential operational complexity, size and cost of such studies, Table 2 present several clinical trial designs that could be considered for Phase 2. Sponsors should consider the potential benefits of alternate trials designs including Bayesian adaptive approaches such as those used for dose finding in the Phase 2 study of lecanemab in early AD [17].

For development candidates that progress to Phase 3, the safety of add-on therapy to an anti-amyloid MAB should be established by allowing participation of a sufficient number of individuals receiving these therapies or conducting a separate trial involving patients required to be on anti-amyloid treatment. It is anticipated that emerging therapies will be used together in clinical practice and the safety of combinations must be established prior to the end of the Phase 3 program.

To establish superior efficacy of add-on therapy over anti-amyloid MAB treatment alone, a sufficiently well powered trial with participants on anti-amyloid MAB therapy alone compared to an anti-amyloid MAB plus the novel add-on agents would be required. Superiority trials of this type may require prohibitively large numbers of participants. Alternative clinical trial designs relevant to Phase 3 are summarized in Table 2.

As anti-amyloid MABs continue to establish a role in the care of patients with early AD it may be more difficult to conduct monotherapy trials. In global regions where approval has not yet been granted regulatory authorization, Phase 1b/2a monotherapy studies can establish safety, target engagement, pharmacodynamic measures, and initial indications of clinical efficacy to support proof of mechanism/proof of concept [18]. In all global regions, there will be many patients who are not candidates for MABs who may be enrolled in monotherapy trials.

4.9. Clinical outcome measures for add-on therapy trials

Clinical outcomes used in add-on therapy trials are the same as those employed in monotherapy trials. Lecanemab and donanemab used the Clinical Dementia Rating Sum of Boxes (CDR-sb) and the integrated Alzheimer's Disease Rating Scale (iADRS), respectively, as primary outcome measures in Phase 3 trials [1,2]. The Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog), Alzheimer's Disease Composite Score (ADCOMS), and Alzheimer's Disease Cooperative Study Activities of Daily Living Scale for mild cognitive impairment (ADCS-MCI-ADL) comprised the secondary outcomes for the Phase 3 trial of lecanemab. Secondary outcomes in the Phase 3 donanemab trial included the ADAS-cog and ADCS instrumental ADL (ADCS-iADL) scale. Alternatives to these conventionally used outcome measures such as the Neuropsychological Test Battery [19] for cognition or the Amsterdam ADL scale [20] for function can be considered. Presentation of the psychometric properties of novel assessments to regulatory agencies is required before integration into clinical trials.

Noncognitive clinical measures that enhance understanding of the therapeutic benefit of combination therapy are available. Aducanumab trials included the Neuropsychiatric Inventory and showed a drug-placebo difference in favor the active therapy [21]. Measures of quality of life and caregiver burden provide insight into treatment ramifications on caregiver and patient lives as shown in the lecanemab Phase 3 trial [2,22]. Funding and reimbursement decisions may be informed by including resource utilization and health outcome measures in trials [23].

Demonstration of superior cognitive benefit of add-on therapy will require demonstration of slowing beyond that observed in anti-amyloid MAB monotherapy trials (Table 1). Establishing superiority will require large, long Phase 3 trials or agents that have large effect sizes.

4.10. Biomarker outcome measures for add-on therapy trials

Biomarkers, particularly for target engagement, are critical for derisking clinical development programs. AD biomarkers are markedly changed by anti-amyloid MABs making their use difficult for assessment of novel add-on therapies. Establishing the biomarker profile of a novel agent in Phase 2 in the absence of an add-on therapy is a key goal of the development program. This is the principal opportunity to understand the biological impact of the novel therapy as reflected in biomarkers in the absence of simultaneous administration of the anti-amyloid MAB. Informed consent to store samples for later studies will allow interrogation of blood or CSF when new questions arise.

Production of a measurable clinical benefit in clinical trials of anti-amyloid MABs requires reduction of amyloid plaque levels on amyloid PET imaging below 15 to 25 Centiloids. All successful agents produce reductions of this magnitude in plaque burden [9]. In addition to the plaque reduction observed on amyloid PET, the Phase 3 trial of lecanemab demonstrated CSF biomarker changes including an increase in Aβ 1-42, decreased Aβ 1-40, decreased total tau, decreased p-tau 181, and decreased neurogranin. There was no drug-placebo difference in

neurofilament light (NfL). In the same study, the plasma Aβ42/40 ratio decreased and tau 181 and glial fibrillary acidic protein (GFAP) decreased, with no consistent change in NfL [2]. In the donanemab Phase 3 study reductions in plasma p-tau 217 and GFAP were observed. There were no changes in the plasma Aβ42/40 ratio or NfL [24]. Reductions in p-tau 217 and GFAP were significantly correlated with the Centiloid changes in plaque amyloid burden observed on PET.

Target engagement biomarkers for the novel agent provide insight into the pharmacologic or biologic activity of the intervention even in the presence of an anti-amyloid MAB. In addition, reductions in p-tau 181, p-tau 217, or GFAP of greater magnitude or with a different time trajectory than the changes observed following treatment with anti-amyloid MABs monotherapy might provide information about the impact of the novel therapy on the underlying biology of AD [8]. When several biomarkers are collected, review of the profile of biomarker effects may reveal differences between changes produced by the novel agent as add-on and those produced by anti-amyloid MAB monotherapy.

Agents that have effects on biomarkers not known to be affected by anti-amyloid MABs such as markers of synaptic dysfunction in CSF may provide information on the mechanisms of novel agents [25]. Fluorodeoxyglucose (FDG) PET or MRI connectivity studies conducted in concert with the initiation of the add-on therapy might provide useful data [26,27].

4.11. Formulation considerations with add-on therapies

Consideration of patient and care partner burden and convenience is critical to successful introduction of new therapies for AD. Patients receiving treatment with an anti-amyloid MAB will receive their treatment by intravenous infusion or possibly via subcutaneous administration. Frequency of dosing may vary between weekly for some subcutaneous formulations to monthly or twice monthly for intravenous therapies. Intrathecal administration of the anti-tau agent BIIB080 is required every three to six-months. Add-on therapies that do not increase patient and care partner burden include oral treatments or antibody or other therapies that could be administered simultaneously with the anti-amyloid MAB. Intranasal therapies might be considered if consistent dosing can be achieved. Early review of formulation alternatives may facilitate market entry of novel treatments introduced as add-on therapies.

5. Discussion

Anti-amyloid MABs represent a new era in the treatment of AD. As the first DTTs for AD, they represent an important milestone in advancing therapeutics for AD and neurodegenerative disorders. The modest efficacy and narrow population for which these agents are approved set the stage for continuing research to identify more efficacious, safer, more convenient, and more broadly applicable therapies. In some cases, new DTTs may replace current monotherapies and in other cases they will be add-on medications provided to patients receiving anti-amyloid MABs [28]. Clinical trials and drug development programs must anticipate the complexities of including patients on anti-amyloid MABs.

Clinicians have been hesitant in adopting new therapies with unfamiliar monitoring requirements. These circumstances create an opportunity for monotherapy of novel compounds when anti-amyloid MABs are not yet perceived as the required standard of care.

Anti-amyloid MABs require substantial healthcare technology integrated into advanced health care systems for their safe and effective administration. Amyloid confirmation, MRI monitoring, and genotyping are required for use of these agents. Many global health care systems will not meet the resource standards required for integration of these new therapies. In some countries, the necessary resources will be available only in academic or urban environments and available only to selected patients. Unavailability of these agents in some global regions creates a geography for conduct of monotherapy trials for novel agents. Phase 2 trials may be conducted in regions where there is limited availability of anti-amyloid MABs. Add-on therapies to MABs may occur preferentially in Phase 3 programs. Treatments tested and shown to be efficacious in low resource global regions should become available in those countries if approved.

Currently available MABs specifically target amyloid-related targets. Approval of DTTs for non-amyloid therapies relevant to AD will inevitably lead to add-on therapy in clinical practice where clinicians are striving to keep their patients functioning at the highest level for the longest time. For this reason, demonstration of safety of add-on therapy is critical to achieve in development programs prior to marketing. Evidence of efficacy of add-on therapies will require a weight of evidence approach that may include non-clinical studies, early- and late-phase trial observations, and registry and real-world evidence. Superiority of combination therapy over anti-amyloid MAB monotherapy may require large, long trials that may not be feasible. With more robust use of anti-amyloid MABs, electronic medical records and claims data will be a source of real-world observations to help inform effectiveness, safety, adherence, and use in a broader population than those participating in clinical trials [29]. Capture of real-world data in registries such as the Alzheimer's Network for Treatment and Diagnostics (ALZ-NET), the International Registry for Alzheimer's Disease and Other Dementias (InRAD), or other available registries represent a critical information-generating strategy when introducing new DTTs and add-on therapies into clinical practice [30].

6. Summary

Lecanemab and donanemab are increasingly used to treat early AD. Approvals are occurring globally and familiarity with use of these agents is leading to their increased use by clinicians. Management of ARIA in community settings is proving to be feasible and there is increasing confidence in the safety of these agents [31]. Several monoclonal anti-amyloid MABs are in Phase 2 and Phase 3 clinical trials indicating that this therapeutic strategy will continue to be a part of the AD therapeutic landscape. The increasing use of anti-amyloid MABs in clinical practice implies that more patients interested in clinical trials of novel agents will be on treatment with these therapies when they enter trials. Strategies for incorporating patients on MABs into trials must be defined and how best to assess the safety and efficacy of add-on therapy must be understood.

Add-on therapy has unique challenges in terms of the timing of treatment with a novel agent after initiation of the MAB, the impact on measures of clinical and biomarker measures, and the interrogation of safety, tolerability, and convenience of the add-on combination. We suggest that introduction of a novel agent be delayed until the patient has been on the highest dose of the MAB for at least 6 months. This will ensure that most ARIA that may occur with MAB therapy has occurred and will not be misattributed to the novel agent. Clinical measures used in combination trials are the same as those used in monotherapy trials with anti-amyloid MABs or other agents. We suggest that biomarker strategies include a robust collection of biomarkers in Phase 2 monotherapy trials prior to allowing add-on therapy. In add-on trials, use of biomarkers not affected by MABs, identification of target engagement biomarkers unique to the novel agent, and inspection of the response profile of biomarkers may indicate whether the magnitude, timing, or trajectory of response differs from those observed in anti-amyloid MAB monotherapy trials. The biology of AD is complex and optimizing the response to therapy will require add-on therapies to the currently available anti- amyloid MABs. Optimizing patient care requires incorporation of add-on strategies into drug development programs.

CRediT authorship contribution statement

Jeffrey Cummings: Conceptualization, Project administration,

Writing – review & editing, Writing – original draft. **Aaron H Burstein:** Conceptualization, Project administration, Writing – review & editing. **Howard Fillit:** Conceptualization, Project administration, Writing – review & editing.

Declaration of competing interest

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

Jeffrey L Cummings reports a relationship with Acadia Pharmaceuticals Inc that includes: consulting or advisory. Jeffrey L Cummings reports a relationship with Acumen Pharmaceuticals Inc that includes: consulting or advisory. Jeffrey L Cummings reports a relationship with ALZpath Inc that includes: consulting or advisory. Jeffrey L Cummings reports a relationship with Annovis Bio Inc that includes: consulting or advisory. Jeffrey L Cummings reports a relationship with Artery Therapeutics Inc that includes: consulting or advisory. Jeffrey L Cummings reports a relationship with Axsome Therapeutics Inc that includes: consulting or advisory. Jeffrey L Cummings reports a relationship with Biogen Inc that includes: consulting or advisory. Jeffrey L Cummings reports a relationship with Biohaven Ltd that includes: consulting or advisory. Jeffrey L Cummings reports a relationship with Bristol-Myers Squibb Company that includes: consulting or advisory. 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Review

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

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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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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

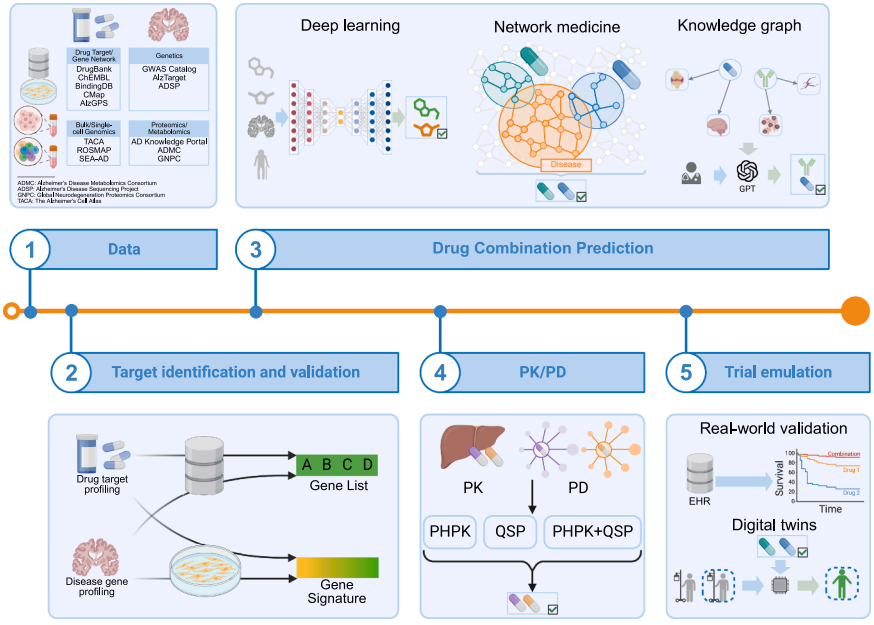

Fig. 1. A diagram illustrating computational framework for rational drug combination design in Alzheimer's disease. The entire process contain (1) high-quality data curation, (2) target identification and validation, (3) drug combination prediction using various computational approaches across deep learning, 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
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

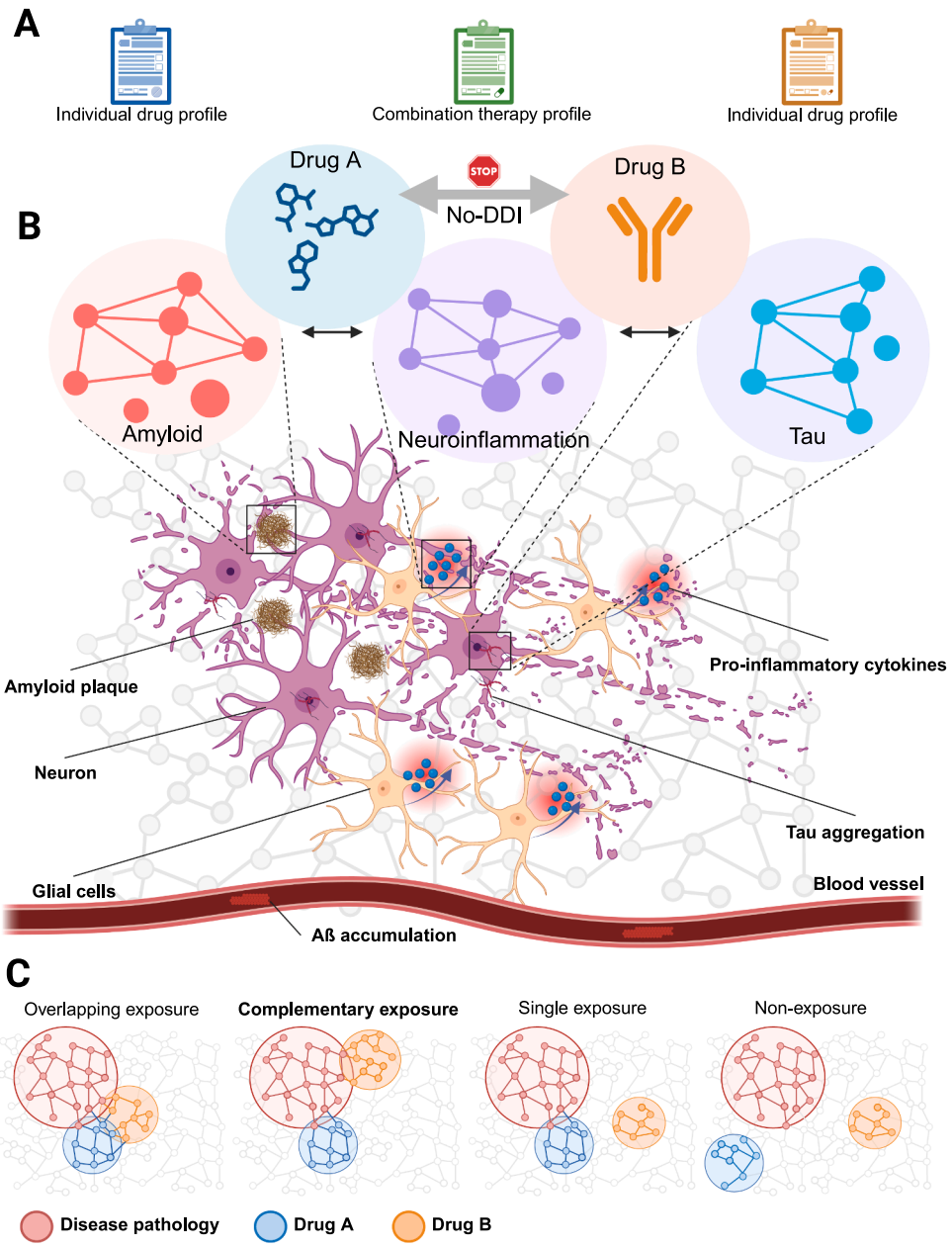

Fig. 2. Conceptual framework of rational drug combination design based on endophenotypes in Alzheimer's disease (AD). (A) Combinations of drugs are prioritized with joint consideration of a drug's disease relevance profile as well as its drug–drug interaction profile. Ideal combinations seek complementary 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

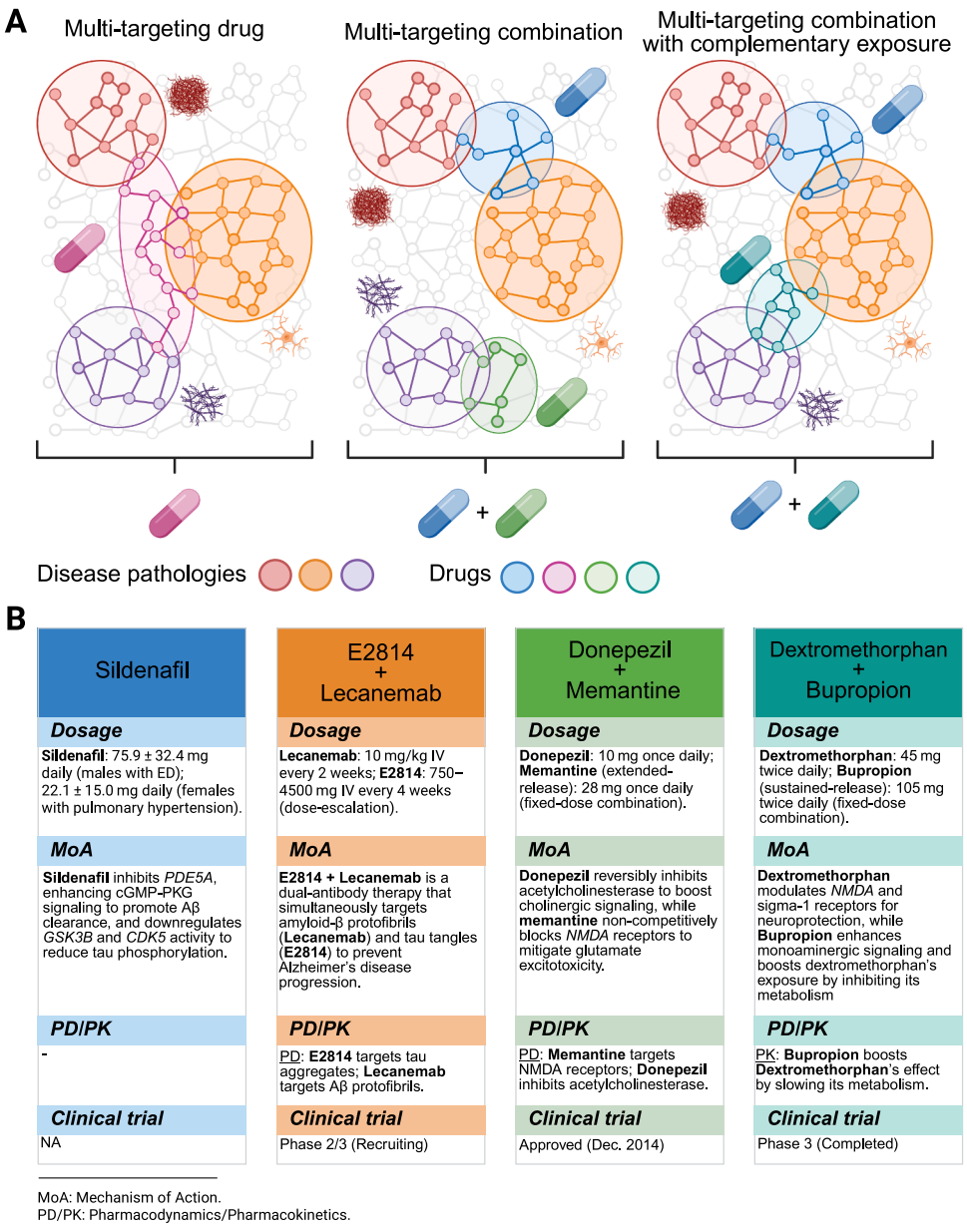

Fig. 3. Illustrative drug combination design patterns and real examples. (A) Conceptual framework of pharmacodynamics-based drug combination strategies targeting Alzheimer's disease (AD) pathologies. Three design patterns are illustrated: (i) *multi-targeting drugs* that affect multiple disease pathologies 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

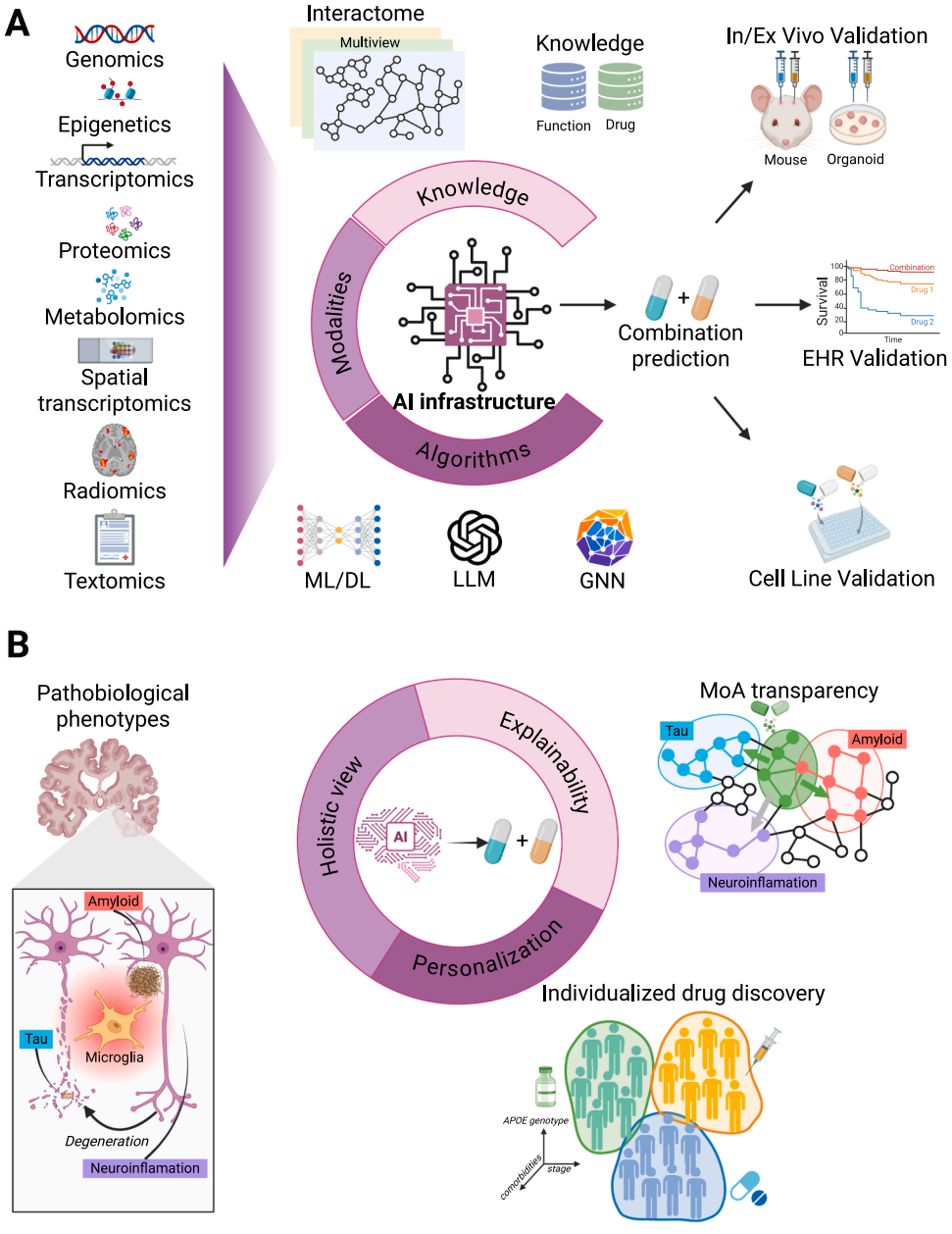

Fig. 4. Prospect for a next-generation framework for drug combination design centered on Artificial Intelligence (AI) and preclinical and clinical validation for Alzheimer's disease (AD). (A) A conceptual AI framework for AD drug combination discovery, leveraging multi-modal data (e.g. omics, clinical, 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.

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Supplementary materials

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Special Article

The impact of recent approvals on future alzheimer's disease clinical development: Statistical considerations for combination trials

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ABSTRACT

Background: A new era of Alzheimer's disease (AD) research is beginning with multiple approved anti-amyloid monoclonal antibodies (mABs). These drugs are currently not widely used, but may be soon, especially at clinical trial sites. Putative disease-modifying therapies (DMTs) may alter the progression rate, potentially reducing our ability to detect effects on top of mABs. Co-administration of amyloid-targeted agents may diminish benefit (antagonism, due to the overlapping mechanism of action); alternatively, complementary treatment mechanisms may increase benefit (synergy).

Method: We consider several clinical trial design scenarios: a 2-arm trial added-on to a mAB, a 2-arm combination compared to double placebo, and a 4-arm full factorial trial. We calculate the required sample sizes for the shortest practical study for secondary prevention (prevention of AD clinical diagnosis in biomarker positive individuals, 2-year study), early AD (18-months), and mild-to-moderate AD (1-year). We consider additivity, antagonism, and synergy.

Result: The expected interaction between investigational and mAB treatment can have a large effect on power and study design. Antagonistic treatment effects often require double the sample size of synergistic effects. The 4-arm scenario required ~10-fold increase compared to a 2-arm combination study.

Conclusion: Studies evaluating investigational therapies as add-on to mABs are complex, and their cost will depend on the interaction between treatments. An inescapable fact in add-on trials is the slower progression of the control arm; and it is difficult to further slow already slow progression. Treatments that are likely to work better with amyloid removal will be easier to study due to their complementary MOA. Symptomatic treatments may require fewer additional subjects than disease-modifying treatments since they are less affected by the presence or absence of mABs.

1. Introduction

1.1. Research setting

The disease modifying treatments (DMTs) lecanemab and donanemab have received full approval from FDA in June 2023 and July 2024 for the treatment of early Alzheimer's disease; and are covered by Medicare and Medicaid for eligible patients. Subsequently, they are now receiving regulatory authorization in ex-US regions, albeit at a slow pace. These treatments usher in a new era for the AD field, with widespread ramifications, including for the design of investigational drug trials.

1.2. Development of combination therapy is urgently needed in AD

AD is a complex disease, likely with more than one pathogenetic mechanism contributing to the onset and progression of the disease [1–3]. Treatment is further complicated by the frequent presence of co-pathologies, such as alpha-synuclein and TDP-43, alongside amyloid and tau pathology. Given this heterogeneity, therapies that target more than one underlying mechanism may be necessary to achieve significant clinical benefit, and combination treatment is a straight-forward approach to target multiple mechanisms.

For example, the approved mABs treatments reduce amyloid burden markedly in the brain, to sub-pathogenic levels in many patients;

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however, this results in only moderate average slowing of cognitive decline[4,5]. Other than amyloid beta accumulation, possible pathogenic mechanisms of AD include p-Tau aggregation and neurotoxicity, nueroinflammation[6], synaptic dysfunction and demyelination, mitochondrial dysfunction, lysosomal dysfunction, lipid abnormalities, insulin resistance [7,8], and more [1–3].

Combination treatments have been at the heart of key medical breakthroughs in the treatment of cancer[9,10] and AIDS[11,12], and about 25 % oncology trials are combination therapy trials[13]. Combination therapies are also commonly used in other complex diseases, including cardiovascular disease[14], pulmonary disease, and autoimmune diseases. Given the complexity of AD, it would not be surprising if therapies that combine drugs with different MOAs may be more efficacious than a single drug that works on a single mechanism. Beyond increased efficacy, combination therapy may offer additional advantages over monotherapy, such as reduced required dosages with maintained efficacy, lower toxicity, fewer side effects, and decreased risk of drug resistance[15].

1.3. Design options (Combination trial and add-on trial)

Combination therapy is when both treatments are included and provided as part of the study. Add on therapy is when patients come to the study already taking some medication that is not the main focus of the study.

When acetylcholinesterase inhibitors (ChEi) were the only available treatments for AD and later when memantine was also available, some AD treatment trials were designed as an add-on to standard of care (ChEi, memantine, both or neither),These add-on trials required the use of existing treatments[16], with examples trails like memantine and ChEi, ginkgo biloba extract EGb 761 and donepezil[17], multivitamin (B_6, B_{16}, and folic acid) and ChEi [18].

For these add-on trials, treatment effects were assessed in two arms, ChEi + investigational therapy and ChEi + placebo. Different designs have been used for investigational drug add-on trials, including 2-arm, 3-arm, and 4-arm designs. A simple 2-arm design allows the approved treatment as a background treatment, which must be stabilized prior to the randomization to add-on either placebo or the investigational drug. Stabilization periods of 2–6 months have typically been used [19–23].

A variation of the simple add-on design is the controlled/sequential add-on design in which treatment naive participants are enrolled. All participants start the approved treatment at the start of the trial for a stabilization period, then the investigational treatment or placebo is added to the approved background treatment based on randomization [24]. Considering that the appropriate use recommendations for Donanemab suggested discontinuation of treatment based on amyloid clearance[25], a sequential add-on trial where the investigational treatment and placebo are administered right after mAB discontinuation could be considered in such a case.

Another variation is the *de-novo* add-on design that also enrolls treatment naive participants but participants are randomized to start both the approved treatment and the investigational treatment or

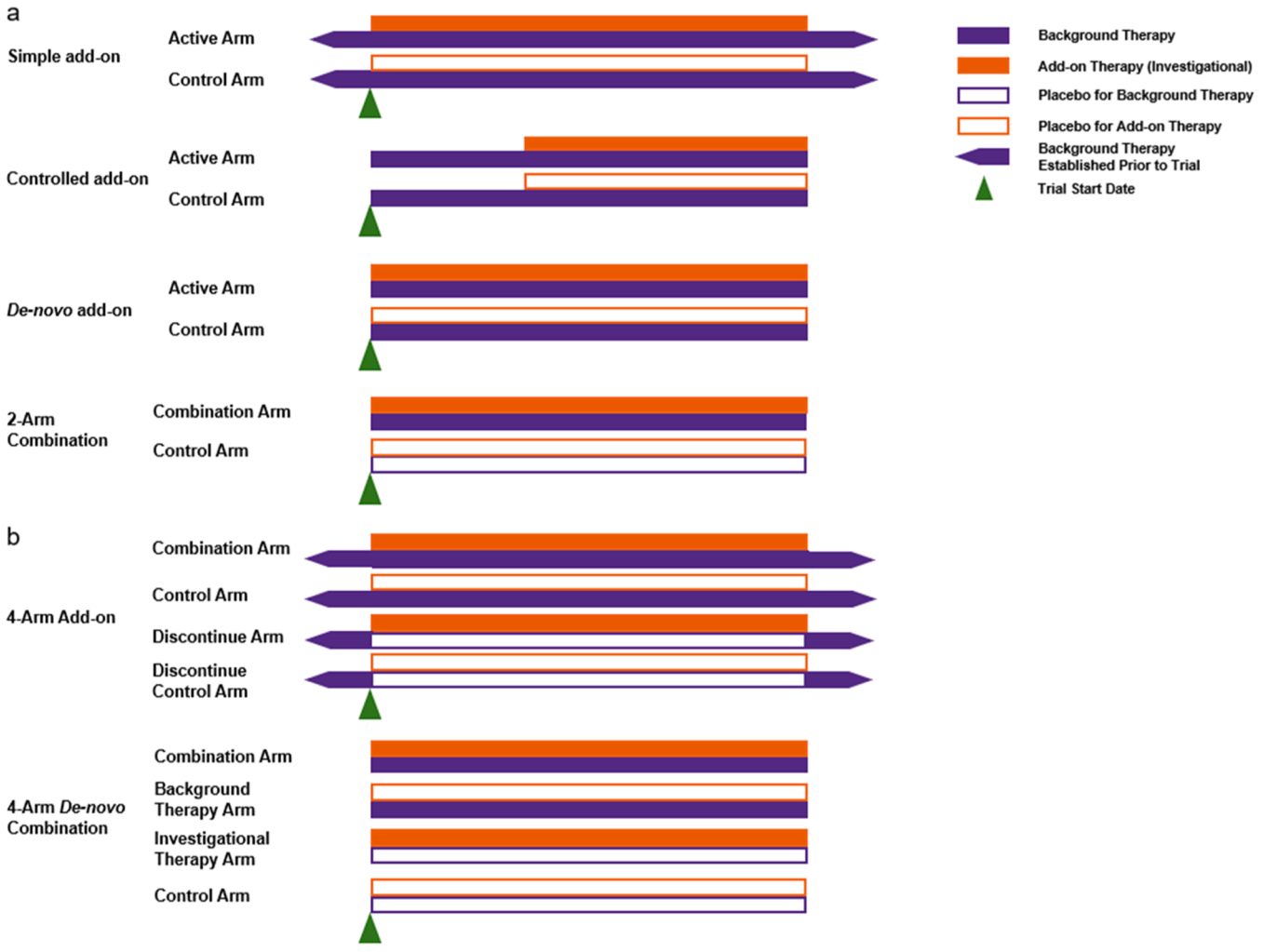

Fig. 1. Example clinical trial designs for add-on and combination trial. a, 2-arm designs; b, 4-arm designs.

placebo at the same time, immediately after randomization [26]. Other variations of these add-on designs include testing multiple doses of the investigational treatment [27,28]. Many other variations also exist and are not enumerated here.

Another option called the 2-arm combination design has a combination treatment arm and a double placebos arm. Examples of 2-arm designs are illustrated in Fig. 1a.

Common implementations of 4-arm add-on designs entail a two-by-two factorial arrangement of treatments: 1) investigational drug + placebo, 2) approved drug + placebo, 3) investigational drug + approved treatment, 4) placebo + placebo. As with the 2-arm design, participants could be de novo or stabilized on the background / approved treatment prior to randomization. The 4-arm design allows testing the following hypotheses: 1) investigational drug vs placebo; 2) investigational drug vs approved treatment, as either a superiority or non-inferiority test; 3) combination treatment vs approved treatment; 4) approved treatment vs placebo as a positive control to assess assay sensitivity; and 5) combination arm vs placebo, although this hypothesis is commonly of less scientific and regulatory interest. Examples of 4-arm designs are illustrated in Fig. 1b

Add-on trials can use 3-arm designs to either include the combination arm and the two single treatment arms[17] or the combination arm, background only arm, and the double placebo arm[29,30]. In the double placebo arm, one placebo matches the investigational treatment, and the other placebo matches the approved treatment.

The choice of design is driven by trial objectives and regulatory considerations. However, these design choices can have major implications on trial size and feasibility. For example, the two-by-two factorial, 4-arm design can provide the most information regarding the various treatment combinations, but at the cost of a larger trial.

The recent approvals of anti-amyloid mABs in AD motivates consideration of trial designs to investigate combination treatments that include an approved mAB treatment and an investigational treatment. The primary aim of this investigation is to assess the sample sizes required and summarize other design considerations for combination trials.

2. Methods

The sample size implications of three combination trial designs (2-arm add-on, 2-arm combination, and 4-arm combination) were investigated across scenarios defined by three disease stages (AD prevention, early AD, and mild-to-moderate AD). Three general types of combination drug effects were investigated: additive, synergistic, and antagonistic.

2.1. Placebo mean to standard deviation ratio (MSDR) for clinical outcomes in different stages

The progression rate and the most prevalent symptoms vary throughout the course of AD [31–33]. The mean to standard deviation ratio (MSDR) is a metric that provides a standardized method to compare magnitude of disease progression across outcomes within a trial and between trials. Mathematically, the MSDR is the mean change from baseline divided by the standard deviation in change from baseline. MSDR is most often applied to the control arm of a trial as an assessment of how much progression the investigational drug has the opportunity to prevent.

Consistent with this, we assumed different primary outcomes for populations at different AD stages. These selections were based on outcomes optimized for the specific populations, even if there has not been universal acceptance of these outcomes by regulators. In practice, slow adoption by regulators of optimized outcomes will lead to larger sample sizes or greater type II error, but for pivotal trials, traditional outcomes may be necessary. For the prevention population (participants have confirmed AD pathology but on clinical diagnosis), the Alzheimer's Prevention Initiative Preclinical Composite Cognitive test (APCC), an optimal composite cognitive test score comprised of seven cognitive tests/subtests is chosen, with an MSDR = 0.34 for 2-year studies [34]. For the early AD population, ADCOMS, a composite clinical outcome for prodromal Alzheimer's disease trials, is chosen, with an estimated MSDR of 0.55 for 18-month trials [35]. For the mild to moderate AD population, the combined MSDR of the Alzheimer's Disease Assessment Scale (ADAS-cog), the Mini-Mental State Examination (MMSE), and Clinical Dementia Rating Sum of Boxes (CDR-SB) is 0.67 for 1-year studies [36].

2.2. Scenarios for treatment interaction

The combined effect of two treatments can be additive, synergistic, or antagonistic, when the effect of the combination is equal to, greater than, or less than the sum of the effects of the individual drugs, respectively.

Table 1 summarizes the % slowing of disease progression for each of the 3 types of combination effects in each of the 3 designs, assuming the investigational treatment and the mAB treatment both have 100 % of the reference effect size (though the actual reference effect size may be large or small), and the synergistic and the antagonistic effects are 30 % higher or lower. The standardized treatment effect (Cohen's D) is equal to the MSDR in the control arm multiplied by the % slowing of the investigational treatment. For example, if MSDR = 0.55 and % slowing = 40 % (similar to the population and slowing of anti-amyloid mAB trials), the Cohen's $D = 0.55 \times 0.40 = 0.22$; if the MSDR = 0.34 and % slowing = 60 % (which may not be unreasonable for a prevention trial), Cohens $D = 0.204$.

The Cohen's D for the various combination arms in each scenario are summarized in Fig. 2. These effect sizes were used to determine power and sample size based on the *t*-test for the treatment contrast at the endpoint visit.

3. Results

3.1. General considerations

Detailed results for each of the three clinical trial scenarios (prevention, early AD, mild-moderate AD) are presented in the following respective subsections. General results that apply to all scenarios are summarized here.

Within scenarios, the effect size for a synergistic treatment effect is always > additive effect, which is always > than the antagonistic effect. Therefore, within every scenario the synergistic effect always has the highest power for a given sample size and the smallest sample size for a

Table 1
Interactions between Investigational treatment and background anti-amyloid mAB.

Scenarios		Effect size (relative to reference)*
Add-on trial (Combination Treatment vs background therapy)	Additive with background therapy	100 %
	Synergistic with background therapy	130 %
	Antagonistic with background therapy	70 %
2-Arm Combination trial (Combination Treatment vs Double Placebo)	Additive	200 %
	Synergistic additive	230 %
	Antagonistic additive	170 %
4-Arm Combination trial (Combination Treatment vs Each Component)	Additive	100 %
	Synergistic additive	130 %
	Antagonistic additive	70 %

* Here we assume each treatment has 100% of an anti-amyloid mAB or other approved treatments (when available), and the synergistic and the antagonistic effects are 30% higher or 30% lower (relative to the mAB or base treatment).

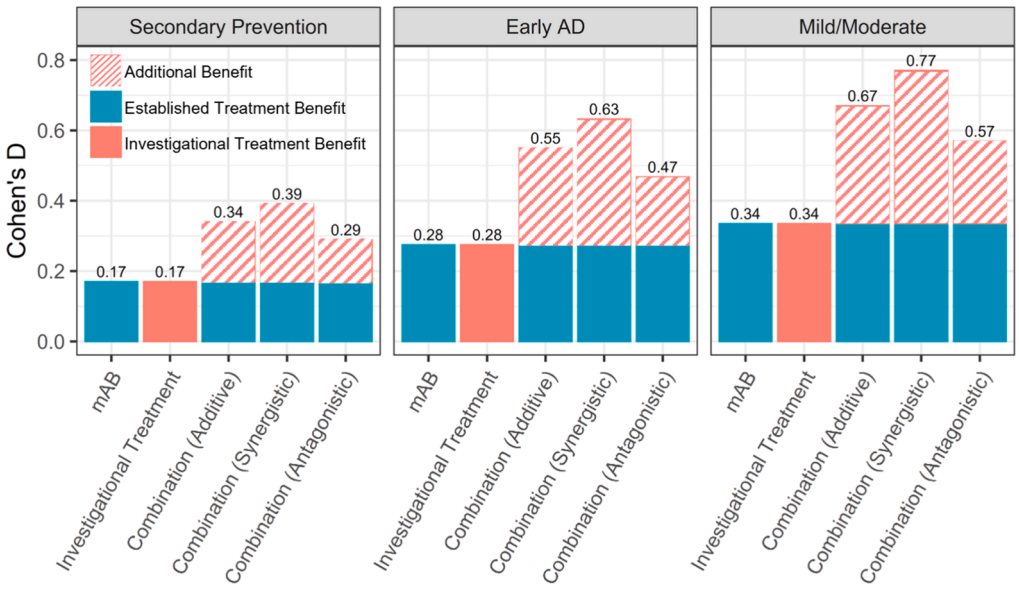

Fig. 2. Demonstration of Cohen's d effect size clinical trial designs with single investigational treatment, add-on investigational treatment to mABs, and 4-arm combination trials in AD populations.

given power.

Commensurate with the MSDRs, within each type of combination drug effect (additive, synergistic, antagonistic), power was greater and sample size lower for mild-moderate AD than for early AD, and early AD had greater power and smaller sample size than prevention.

3.2. Prevention population

Results are summarized below for the prevention trial scenarios (2-year treatment duration and MSDR = 0.34). Table 2 summarizes the number of patients needed for each arm in the trial and the total for the trial under specific conditions. Fig. 3 depicts sample sizes required across a range of effect sizes as described by % slowing.

A, Sample size (per group) vs treatment effect (percent slowing relative to placebo) in single group or add-on trial designs, assuming 80 % power. B, Power vs treatment effect in single group or add-on trial designs, assuming 100 completers per group. C, Sample size (per group) vs treatment effect in 4-arm combination trials, assuming 80 % power.

Table 2
Sample size calculation for 2-arm combination, 2-arm add-on, and 4-arm combination trial designs in AD prevention population for 2-year studies.

Scenario	N Per Group 80 % power	Total N 80 % power	Power with 100 per arm
2-Arm Add-on Trial			
Single Treatment is additive	545	1090	22.2 %
Synergistic: + 30 %	323	646	34.2 %
Antagonistic: - 30 %	1111	2222	13.1 %
2-Arm Combination Trial (Combination Treatment vs Placebo)			
Additive Treatments	137	274	66.7 %
Synergistic: Additive + 30 %	104	208	78.5 %
Antagonistic: additive - 30 %	190	380	52.9 %
4-Arm Combination Trial (All 4 comparisons – Combination vs each, each vs Placebo)			
Additive	882	3528	<1 %
Synergistic: Additive + 30 %	741	2964	1 %
Antagonistic: additive - 30 %	1477	5908	<1 %

Assuming a 50 % effect size on disease progression slowing for 2-year studies. The last column assumes 100 completers per arm.

3.3. Early AD population

Results are summarized below for the early AD trial scenarios (18-month treatment duration and MSDR = 0.55). Table 3 summarizes the number of patients needed for each arm in the trial and the total for the trial under specific conditions. Fig. 4 depicts sample sizes required across a range of effect sizes as described by % slowing.

A, Sample size (per group) vs treatment effect (percent slowing) in single group or add-on trial designs, assuming 80 % power. B, Power vs treatment effect (percent slowing) in single group or add-on trial designs, assuming 100 completers per group. C, Sample size (per group) vs treatment effect (percent slowing) in 4-arm combination trials, assuming 80 % power.

3.4. Mild-moderate AD population

Results are summarized below for the mild-moderate AD trial scenarios (12-month treatment duration and MSDR = 0.67). Table 4 summarizes the number of patients needed for each arm in the trial and the total for the trial under specific conditions. Fig. 5 depicts sample sizes required across a range of effect sizes as described by % slowing.

A, Sample size (per group) vs treatment effect (percent slowing) in single group or add-on trial designs, assuming 80 % power. B, Power vs treatment effect (percent slowing) in single group or add-on trial designs, assuming 100 completers per group. C, Sample size (per group) vs treatment effect (percent slowing)

4. Discussion

In this analysis, we investigated trial design options when combining an investigational treatment with a standard treatment. The specific findings of this study apply to the scenarios investigated; however, the basic approach can be extended and generalized, for example, to any mechanism of action for background and investigational treatments. The concepts of synergy, additivity, and antagonism apply universally to combination treatments even though the type and magnitude of combination effect will vary.

Among the 2-arm combination, 2-arm add-on, and 4-arm combination trial designs, 2-arm combination trials had the greatest power and required the smallest sample sizes under the conditions assumed here. This finding was consistent across all AD populations investigated. These

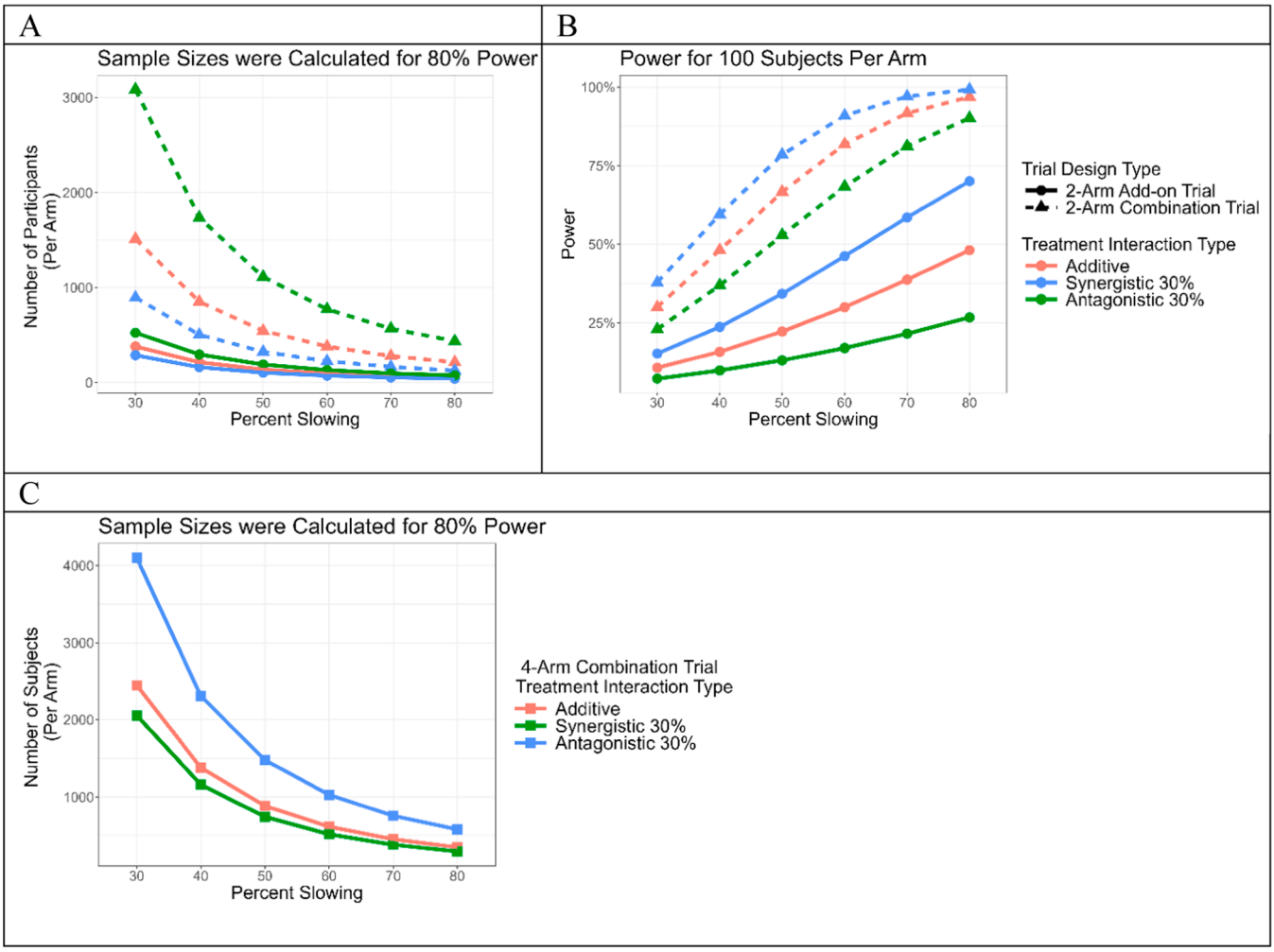

Fig. 3. Sample size requirements with different treatment effect sizes for 2-arm combination trials, 2-arm add-on trials, and 4-arm combination trials in AD prevention population.

Table 3
Sample size calculation for 2-arm combination, 2-arm add-on, and 4-arm combination trial designs in early AD population for 18-month studies.

Scenario	N Per Group 80 % power	Total N 80 % power	Power with 100 per arm
2-Arm Add-on Trial			
Single Treatment is additive	209	418	49.0 %
Synergistic: + 30 %	124	248	71.1 %
Antagonistic: - 30 %	425	850	27.2 %
2-Arm Combination Trial (Combination Treatment vs Placebo)			
Additive Treatments	53	106	97.2 %
Synergistic: Additive + 30 %	41	82	99.4 %
Antagonistic: additive - 30 %	73	146	90.8 %
4-Arm Combination Trial			
Additive	338	1352	5.8 %
Synergistic: Additive + 30 %	284	1136	12.1 %
Antagonistic: additive - 30 %	565	2260	1.8 %

Assuming a 50 % effect size on disease progression slowing for 1.5-year studies. The last column assuming 100 completers per arm.

results should be unsurprising given that 2-arm combination trials compare the combined effect of two treatments to placebo, creating the greatest expected difference in effect between treatment arms, and 4-arm combination trials have the smallest expected difference in effect size between arms and the most number of arms; however, these are important concepts for development programs to consider when determining the direction of development. For instance, there may be scenarios where a 4-arm combination trial is the most efficient design to address the current needs of a development program, but preference should usually be given to smaller more focused trials, when possible.

2-arm add-on studies should be considered for an investigational treatment in an environment where approved treatment is becoming common. 2-arm combination trials are suitable for treatments with low risk of side effects, and when drugs are being considered for alternative indications. Scenarios to consider four-arm studies include when multiple questions are necessary to move development forward, especially when treatment interactions are likely both with respect to efficacy and safety.

By definition, a synergistic effect yields larger effect sizes than an additive effect, which is larger than an antagonistic effect. In the scenarios investigated here, power and sample size varied markedly by type of treatment interaction. An antagonistic effect (additive effect – 30 %) resulted in up to double the sample size for the same power compared with an additive effect. The difference in sample size between antagonistic and synergistic scenarios was as much as 3–4-fold increase.

These sample size implications highlight the importance of understanding if, and if so how the investigation drug interacts with the standard / background therapy. Therefore, as much information as is feasible should be leveraged from pre-clinical and early phase clinical

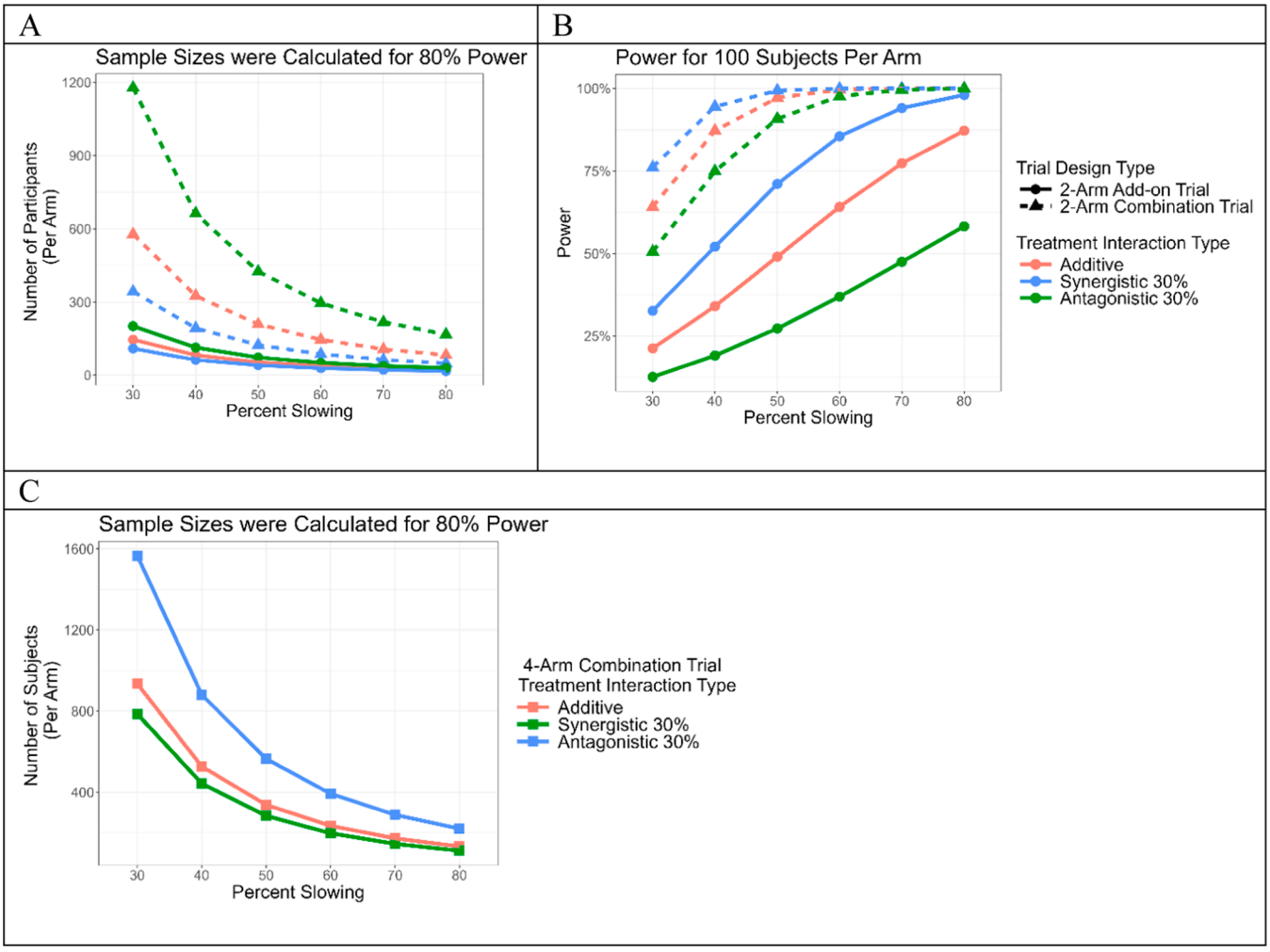

Fig. 4. Sample size requirements with different treatment effect sizes for 2-arm combination trials, 2-arm add-on trials, and 4-arm combination trials in early AD population.

Table 4
Sample size calculation for 2-arm add-on, 2-arm combination, and 4-arm combination trial designs in mild to moderate AD population for 1-year studies.

Scenario	N Per Group 80 % power	Total N 80 % power	Power with 100 per arm
2-Arm Add-on Trial			
Single Treatment is additive	141	282	65.4 %
Synergistic: + 30 %	84	168	86.5 %
Antagonistic: - 30 %	287	574	37.8 %
2-Arm Combination Trial (Combination Treatment vs Placebo)			
Additive Treatments	36	72	99.7 %
Synergistic: Additive + 30 %	28	56	>99.9 %
Antagonistic: additive - 30 %	50	100	98.0 %
4-Arm Combination Trial			
Additive	228	912	18.3 %
Synergistic: Additive + 30 %	192	768	32.1 %
Antagonistic: additive - 30 %	381	1524	6.1 %

Assuming a 50 % effect size on disease progression slowing for 1-year studies. The last column assuming 100 completers per arm.

studies to anticipate either additive, synergistic, or antagonistic effects for the two treatments. In addition, studying a novel therapy alone in a phase 2/ proof of concept study provides critical information for study design. Although this investigation focused on efficacy considerations, the possible interaction of the two treatments in a combination is also critically important to safety.

Although sample size is a key consideration for combination trials, other operational issues are also important to consider. For example, with ≥ 2 active treatments, multiple placebos are needed to blind each active arm; inclusion and exclusion criteria and adverse event management and reporting must factor in both active arms.

The 4-arm combination trial allows testing multiple hypotheses simultaneously: 1) investigational drug vs placebo; 2) combination treatment vs standard treatment; 3) investigational drug vs standard treatment, either in a superiority or non-inferiority testing scheme; and 4) standard treatment vs placebo as a positive control to assess assay sensitivity of the trial. However, the total sample size required for such studies is formidable. Given the common scenario where many sites in a trial will enroll a small number of patients, many sites will not have patients randomized to every arm, creating a confounding of site with treatment, which can increase variability in the data, thereby diluting the treatment signal and leading to need for an even larger sample size. Studies requiring such large sample sizes may benefit from Bayesian or other adaptive sample size determination, but these designs should be discussed with regulators prior to use.

In inescapable fact of combination trials that use an approved

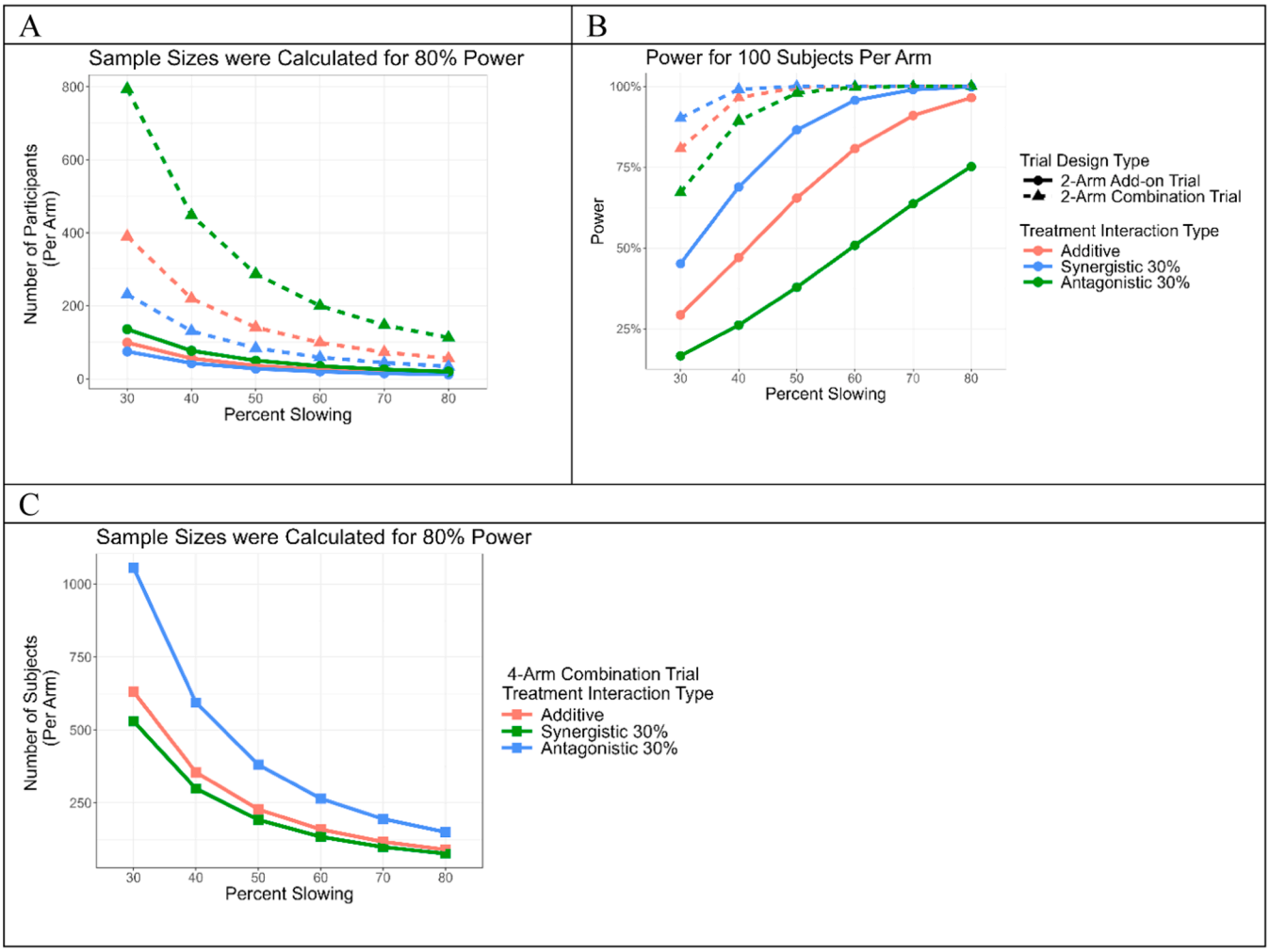

Fig. 5. Sample size requirements with different treatment effect sizes for 2-arm combination trials, 2-arm add-on trials, and 4-arm combination trials in moderate to mild AD population.

treatment as the control arm, the control arm will have less progression than a placebo arm and therefore sample sizes for a given level of power will be larger than with placebo control.

4.1. Considerations of treatment interaction in combination treatment

An important consideration for combination trials is the possible interaction between two treatments. As our results suggest, the effect size is greater with synergistic interaction and therefore easier to detect in the add-on or combination trials. Whereas antagonistic interaction makes it harder to detect an effect and requires a larger sample size. Factors influencing interactions of combination treatment include Mechanism of Action (MOA), pharmacokinetic, and pharmacodynamic. Oncology trials with combination treatment targeting the same pathway may result in antagonism or increased toxicity [37–39]. To inform assumptions in sample size determination, early phase pharmacokinetic and pharmacodynamic studies are recommended, since it may lend insight into the nature of the combination drug effect, for example, is drug absorption, distribution, and/or elimination of each drug influenced by the other; or are effects on pharmacodynamic biomarkers additive or synergistic. Further consideration should be given to the merits of evaluating novel investigational drugs as monotherapy to understand the effects of the individual agent on biomarkers and clinical outcome measures, thereby providing information to enable the design of later stage add-on or combination trials.

Declaration of competing interests

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

Suzanne Hendrix reports the APC fee for this publication was provided by Alzheimer's Drug Discovery Foundation. Suzanne Hendrix reports a relationship with Pentara Corporation that includes: employment and equity or stocks. Samuel P Dickson, Craig Mallinckrodt, Chenge Zhang reports a relationship with Pentara Corporation that includes: employment. Aaron H Burstein, Laura Nisenbaum, Howard M Fillit reports a relationship with Alzheimer's Drug Discovery Foundation that includes: employment. 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.

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Special Article

Statistical innovations in clinical trial design with a focus on drug combinations, factorials, and other multiple therapy issues

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ABSTRACT

Statistical methods in clinical research tend to become entrenched. Innovations threaten the status quo. The "right way" becomes frozen in lore. This is so even when the "right way" is not best. "Statistical significance" and the associated requirement of "high power" is an example. This attitude is an impediment to efficient design. Willingness to address some design issues with moderate power enables building highly informative and highly efficient clinical trials. This article considers several types of clinical trials, including dose-finding, combinations, and factorial designs. Bayesian adaptive methods are used to show that trials can be made more efficient and more informative. Surprisingly, the approach is consistent with many attitudes of the widely regarded "Father of Modern Statistics," R.A. Fisher. Fisher was anti-Bayesian in rejecting its subjective interpretations. But Fisher and Bayes come to the same conclusion in many applied matters. Fisher invented factorial design. Its principal attraction for him was enabling addressing two or more questions with a single experiment. He complained about attitudes that hindered progress: "No aphorism is more frequently repeated in connection with field trials [and clinical trials], than that we must ask Nature few questions, or, ideally, one question at a time… this view is wholly mistaken." Fisher's primary analysis required modeling and making assumptions. For example, his first analysis in a factorial setting assumed no interactions among the factors. He investigated possibilities of interactions but he did not see the need for doing so with high power.

1. Introduction

This article addresses recent modifications in statistical thinking regarding designs of clinical trials. The focus is on Alzheimer's disease (AD) but informed by learnings in other diseases. The final analyses can be Bayesian, frequentist, or a combination of the two.

Bayesian approaches are being increasingly used in clinical trials. They are enabling revolutionary modifications in the building and running of trials. Understanding today's clinical research requires some understanding of the differences in statistical philosophy and some understanding of the evolution of both approaches in influencing each other. The U.S. FDA has played a critical role in understanding innovation and in facilitating the introduction of Bayesian ideas in drug development. Health authorities outside of the U.S. are not opposed to such innovations but they have not taken leadership roles in effecting and perfecting them.

Building a trial that adapts to accruing information is natural within the Bayesian approach. Bayes' rule updates knowledge from one observation to the next. It is ideal for predicting future results, given the currently available results and the future course of the trial's prospective design. The frequentist approach can do neither.

The traditional statistical regulatory requirement of controlling type I error rate, usually to no greater than 2.5 %, is not part of the history or tradition of a Bayesian approach. But controlling type I error is always possible in a Bayesian trial by adjusting its design or analyses using simulations and trial and error. The FDA specifically addresses this approach for complicated trials with many types of adaptations in their Complex Innovative Designs (CID) initiative[1]. Programming clinical trial simulations requires detailed descriptions of the prospective design.

As a guideline, an automaton must be able to conduct the trial. Actually, an automaton does conduct the trial, electronically, by simulating it millions of times before it is actually run. When testing a null hypothesis of a treatment's effect, the proportion of simulations showing a positive effect is the design's type I error rate. The proportion of simulated trials that show a positive treatment effect in its primary analysis is the trial's statistical power when the simulations assume a positive treatment effect[2]. The focus of the present article is when there are many other questions addressed during the trial. For example,

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many arms (perhaps some of which involving combination therapy) may have been considered by the design but were not selected for the primary analyses. The primary analysis recognizes the various adaptations along the way. These adaptations may affect the trial's overall type I error rate and are considered in the calculations. However, the individual adaptations do not require high power.

The Bayesian approach can be used to build efficient and accurate clinical trials. Considering a particular adaptive feature will be helpful and illustrative for several reasons. A suggestion by W.R. Thompson in 1933 was to use a Bayesian calculation to set randomization probabilities in a two-armed clinical trial[3]. The next patient is assigned to an arm with probability that is "some monotone increasing function of the current [Bayesian] probability that it is the better of the two arms."[3] Thompson was motivated by ethics: "If such a discipline were adopted, then though it were not the best possible [strategy], it seems apparent that a considerable saving of individuals otherwise sacrificed to the inferior treatment might be effected."

Using a Bayesian calculation does not make the trial Bayesian. It would be Bayesian if the final analysis of treatment effect is its posterior probability distribution[4,5].

Thompson was using Bayesian statistics as a tool. To underline the point, statistician Peter Armitage once addressed the role of R.A. Fisher in the first use of randomization in a clinical trial. The trial addressed whether streptomycin improved the symptoms of tuberculosis. It was designed and conducted by A.B. Hill and the UK Medical Research Council (MRC). While working at the Rothamsted Experimental Station from 1919 to 1933, Fisher made countless contributions to statistical theory and practice. One was his invention of and promotion of randomization[6]. Another was his invention of factorial design of experiments, a subject considered below.

This is Armitage in 2003: "I know of no written comment by [R.A. Fisher] on clinical trials, although Hill once remarked to me that Fisher had suggested to him that randomization proportions should be altered dynamically as a function of the *P*-value from a significance test, so that as the difference became more significant a smaller proportion of patients received the apparently inferior treatment. …It may be that in the 1930s Fisher thought that doctors would never accept controlled experimentation, and he may even have had ethical objections to the idea."[7] As indicated earlier, Fisher was not a Bayesian. But he was obviously aware of Thompson's work. Fisher simply replaced Thompson's Bayesian probability with a frequentist measure: *P*-value. Back in the 1930s both Thompson and Fisher would have struggled to control type I error for such an adaptive clinical trial without the availability of simulations using modern computers.

2. Bayesian clinical trials

Bayesian and frequentist approaches are inverses of each other (see Table 1). For example, *P*-values are conditional probabilities (of results as or more extreme than the observed results) assuming that the null hypothesis is true. The Bayesian analog is also a conditional probability, but the inverse. It is the probability of the null hypothesis conditioning on the data actually observed in the trial. Bayes' rule "flips the conditionals." It also differs by excluding the seemingly irrelevant "more extreme" data.

A trial's type I error rate is prospective. It is a characteristic of the trial's design but not of its outcome. A *P*-value is the frequentist outcome measure analogous to type I error rate. But calculations of type I error rate can include the effects of Bayesian-driven interim analyses and decisions such as Thompson's adaptive randomization procedure.

The Bayesian approach is inextricably tied to decision-making[8]. Implications of experiments vary with their goals. For example, clinical trial designs should depend on the disease, including its prevalence now and in the future. Consider AD versus

Tay-Sachs disease (TSD). AD affects more than 7 million people in the US and kills over 120,000 of them. On the other hand, infantile TSD is a fatal, autosomal recessive genetic disease that affects fewer than 50 newborns per year in the US.

Table 1
Comparison of bayesian and frequentist approaches in designing and analyzing clinical trials.

Characteristic	Bayesian	Frequentist
Inferential unit	Patient (nested within trial)	Trial
Inferential measure	Probability distributions of parameters and hypotheses	*P*-values and confidence intervals
Probability applies to what?	All uncertainty, including hypotheses and future results	Data: assuming a particular hypothesis
Update probabilities of parameters	Frequently; as needed, including after each observation	Not applicable
Predicting future data (including patients within trial)	Based on current data and outside-trial information	Assumes particular value of unknown parameters
Number of questions addressed by trial	Any	Preferably one
Modeling	Lots of modeling, including of individual patients	Minimal
Decision analysis	Utilities are fundamental and integral to the approach	Awkward

Testing hypotheses and developing generalizable knowledge may be reasonable for AD. Indeed, randomizing hundreds or even thousands of patients with AD in a double-blinded trial while controlling type I error may be an approximate solution to the decision analysis problem. For TSD, on the other hand, randomizing in a clinical trial would be not only logistically difficult and may be unethical. For rare diseases quite generally, randomizing hundreds of patients in a clinical trial is impossible and controlling type I error rate is irrelevant.

A better strategy for both AD and TSD—and for all diseases—is using adaptive designs. One adaptation is increasing the trial's sample size, if necessary—smaller to get a compelling answer sooner, larger to get a stronger answer in the final analysis. The design should accommodate to the information accumulating in the trial[9–14].

Accumulating information includes longitudinal outcomes of individual patients. In AD, a therapy that prolongs survival would be expected to slow progression as measured by clinical markers or biomarkers such as amyloid plaques. Addressing correlations among the various outcomes serves many purposes. One is to enable more accurate imputations for missing data[15]. As a special case of missing data, many patients in AD trials are censored. Correlations among longitudinal outcomes in the trial, depending on therapy, would help in making Bayesian probabilistic predictions of times of death for patients who are still alive at the final analysis of the trial. Symptoms of TSD involve diminution of the senses, including the ability to move. Similarly, a therapy that prolongs survival would be expected to show an earlier effect on the symptoms of the disease, but not always. Bayesian longitudinal modeling is all about reducing uncertainty in the primary outcome measures.

Possible adaptations for AD trials include dropping arms in combination trials with factorial designs (see Section IV). They also include re-estimating sample sizes and adjusting randomization probabilities. Such adjustments include the possibility of setting an arm's randomization probability to 0, which means pausing accrual for the arm and possibly stopping its accrual permanently[15]. For TSD, the optimal adaptive design is simple, and I hope it is obvious. When a new investigational therapy is proposed, it should be assigned to patients (with no randomization) until the death rate shows that it is not an improvement over the historical standard of care. "Standard of care" is itself updated over time based on several factors, possibly including availability of

therapies not currently considered in the trial.

3. Bayesian adaptive platform trials

I-SPY 2 was a phase 2 adaptive Bayesian platform clinical trial in neoadjuvant breast cancer. It ran from 2010 to 2022. It used many statistical innovations as listed in

Table 2. Details are in the references[1,4,5,12–14,16]. How a revolutionary trial such as I-SPY 2 came into being is arguably more important than what the trial was.

Laura Esserman, MD, MBA, was the PI of I-SPY 2. My role was statistical design and serving as the trial's co-PI. Dr. Esserman was an enthusiastic champion and fellow disrupter. The trial would not have been successful without Dr. Esserman's advocacy and strong push for innovation. Others who were instrumental in the formative stages of I-SPY 2 were Janet Woodcock, MD, director of the FDA's Center for Drug Evaluation and Research (CDER), and Anna Barker, PhD, former deputy director of the National Cancer Institute.

I-SPY 2′s design has served as a prototype for platform trials in a variety of diseases, including registration trials in oncology. It was also the model for IMI's EPAD—see below. The design of I-SPY 2 and its descendants are complicated and were made possible by modern improvements in Bayesian statistical software and computer hardware. As indicated above, the FDA recognized complicated designs for registration under the rubric CIDs[1]. I-SPY 2 was a prototype for CIDs, even though it was not itself a registration trial.

The design of I-SPY 2 was itself an experiment, in effect it was designing a trial starting from scratch. We bypassed standard approaches. Drs. Esserman, Woodcock, Barker, and initial funding from the Foundation for the National Institutes of Health were essential. The design was based on multiarmed bandit problems[17,18]. The goal was to treat trial participants effectively while learning efficiently and accurately about the effects of the various therapies [17,18], especially therapies that are effective. One proposal for such a design was Thompson's[3]. The experience of using response-adaptive randomization in scores of trials conducted in the early 2000x at MD Anderson Cancer Center was also essential[19,20].

The FDA's support for I-SPY 2 and beyond I-SPY 2 was instrumental, especially Dr. Woodcock's support. In the case of I-SPY 2 and GBM AGILE, the FDA has encouraged and indeed led innovations. In an article on master protocols, Woodcock and LaVange advertised I-SPY 2 as a prototypic trial[16]. For example: "Innovative aspects of the I-SPY 2 trial design include response-adaptive randomization to assign patients to the most promising treatment or combination of treatments in their respective molecular breast-cancer subgroups…while maintaining a sufficient number of patients assigned to the standard of care, shared use of control patients across treatment comparisons, and Bayesian decision rules to determine whether or when therapies with low probabilities of success or side effects should be discontinued and therapies with high probabilities of future success…should advance for further study."[16]

As indicated above, I-SPY 2′s innovations were driven and facilitated by a Bayesian decision-analytic approach. The trial was successful in using its innovations for the benefit of patients both in the trial and after the trial. Nine of the 23 investigational therapies graduated ready for phase 3, representing most of the trial's 10 prospectively defined, molecular marker-defined signatures. Four of the nine graduates have since received marketing approval within molecular subtypes of adjuvant or neoadjuvant breast cancer. But there's something for everyone (see Table 2). For example, investigational therapies that did not graduate had a thorough phase 2 randomized evaluation in the various molecular subtypes of the disease along with a large-sample-size common control arm.

I-SPY 2 ended in 2022. It was replaced by a very different trial called I-SPY 2.2 that I did not support[21].

The I-SPY 2 trial set a standard for Bayesian platform trials, including in Alzheimer's disease. According to the Innovative Medicines Initiative (IMI) in 2015:

> "Innovative clinical trial designs. The definition and implementation of innovative trials to accelerate access to efficient and safe medicines is of major interest to industry, regulators and patient organizations. Inspired by the I-SPY initiative, the EPAD consortium will develop an adaptive design in a proof-of-concept trial for early intervention in Alzheimer's disease."[22]

Despite the optimism expressed by the IMI, the European Prevention of Alzheimer's Dementia (EPAD) story was mainly negative. However, it

Table 2
Innovative features of I-SPY 2. These features apply regardless of disease and endpoints.

Adding and dropping arms. I-SPY 2 was designed to be potentially never-ending, although it did end in 2022. Arms in the trial would stop accruing patients when they graduated to phase 3, stopped for futility, or reached a predetermined maximum sample size. In all cases, we followed patients and kept confidential the fact that the arm had stopped accruing patients until all the arm's patients were through surgery.
Collection of basket trials. Patients were assigned to one of eight subtypes defined by three molecular tumor markers: hormone receptor status (HR), HER2 receptor status (HER2), and MammaPrint (MP). Investigational arms were evaluated in up to 10 signatures that are combination patient subtypes and that are possible clinical indications.
Definition of Type I error. The basket aspect of the investigational arms meant that there are several possible types of error for each arm. For example, an arm may graduate in a signature for which some subtypes are correctly positive, but others are incorrectly positive. That's not a type I error. In I-SPY 2, I defined a false-positive conclusion as the case when the concluding signature contained no patients who would benefit from the therapy.
Bayesian predictive probability of success in a future phase 3 trial. Adaptive randomization was based on these predictive probabilities. Stopping accrual because of graduation to phase 3 or futility was based on the Bayesian predictive probability of future success.
Continuous learning and Bayesian updating. Each month we calculated the current distributions of pCR rates for all subtypes and all possible signatures for all arms in the trial. We used these distributions to calculate predictive probabilities and, in turn, the assessment of each investigational arm's status in the trial. This included monthly updates of each arm's randomization probabilities and decisions regarding graduation to phase 3, dropping for futility, and stopping accrual at the arm's maximum sample size.
Common control arm (by patient subtype). Investigational arms in I-SPY 2 were compared against a common set of controls, depending on patient subtype. The final analysis of each investigational arm was its Bayesian probability of superiority to control for the primary endpoint of pCR for each signature.
Time machine[34,35]. Patients were assigned to the control arm with 20 % probability unless there was only one investigational arm in the subtype, in which case randomization was 1:1. The control cohort for an investigational arm includes all concurrently randomized controls plus all previously randomized controls. However, the outcomes of the previous non-concurrently randomized controls were adjusted and partially discounted for time trends in the trial. The time trends were assessed for all the arms in the trial, including the other investigational arms. The result was that we built a large data bank of controls that was typically an order of magnitude greater than the total number of patients in the investigational arms, with statistical power much, much greater than typical phase 2 cancer trials.
Longitudinal model of disease burden as auxiliary endpoint[5]. We built a model that related reductions in tumor volume during neoadjuvant treatment, depending on patient subtype. We used historical data from I-SPY 1 but updated the model using I-SPY 2 patients who had experienced surgery. At each analysis epoch, we calculated the probability of achieving pCR for each patient in the trial who had not yet had surgery. We used multiple imputation to find the probability distributions of all the pCR rates for the arms in the trial [4,5].
Nested partial factorials. The continuing control arms of I-SPY 2 enabled addressing combination therapies. One of the initial arms in the trial was AbbVie-sponsored veliparib + carboplatin (VC)[5]. Its successful graduation led to a trial that isolated the effects of V and C[36].
Use of computer simulation to assess design operating characteristics. Traditional statistical designs of clinical trials include type I error rate and statistical power. They should also be addressed in Bayesian trials, especially type I error, if only to preserve continuity with traditional trials.

made important contributions and helped the community understand the difficulties in running a platform trial in AD. The IMI (now the Innovative Health Initiative, or IHI) arranged for generous funding for the EPAD consortium (that included Berry Consultants whom the IMI selected in a competitive process). From 2015 to 2020, the EU contributed 26 M € and the European Federation of Pharmaceutical Industries Associations (EFPIA) contributed another 27 M € of the total 59M € in EPAD funding[22]. The development of EPAD floundered until October 2020 when it failed.

According to its website, "EPAD was a unique collaborative research effort. Our 39 partners across Europe were committed to transforming our understanding of Alzheimer's disease."[22] There were identifiable reasons for EPAD's ultimate failure, but the details are not public. However, the impact of the COVID-19 pandemic did not help, nor did Brexit. Also, having 39 partners in a trial may be wonderful from several perspectives, but a developmental process can be dysfunctional if some of the partners are competitors. This is so even if they have equal shares in making the project successful. There can be too many cooks.

Platform trials have many stakeholders. A lesson from EPAD is that it is difficult to build a platform trial that promises rewards for every stakeholder. Adequate funding from philanthropy, government, and industry is essential but not sufficient. A corollary is that the design must be flexible in terms of patient population and patient subpopulations for the individual treatment arms. Moreover, the design should be flexible in terms of issues such as sample size and statistical power. The trial could be registrational for some arms and pre-registrational for other arms and post-registrational for still other arms. Although the trial must have a master protocol, each treatment arm that enters the trial must have its own appendix, and the master protocol should state explicitly which aspects of an arm's appendix can supersede those aspects of the master protocol.

4. Investigating multiple therapeutic issues

A typical empirical researcher frequently asks this question: "Is your observation statistically significant?" The questioner is asking if the associated *P*-value is less than 0.05. If so, then the questioner and others in the audience accept the observation as "real." Thus, they conclude that the experimental treatment is superior to control, or that a biomarker subgroup has a greater risk for a particular disease than the larger population, etc. If the *P*-value is greater than 0.05, then the reaction is usually that the observation is spurious.

There are many flaws with such reasoning. One is that, regardless of what interpretation one gives to a *P*-value, there is nothing magical about the threshold value of 0.05. Simply put, statistical significance cannot substitute for truth. Moreover, in a decision-making approach, there can be no single threshold for judging significance.

Asking many questions in a clinical trial raises statistical issues that are widely regarded to be problematic. They are almost always less problematic than researchers think. Some feel that merely asking many questions of data is a problem. That feeling becomes part of the culture, to the detriment of science[23].

> R.A. Fisher weighed in regarding these issues: "No aphorism is more frequently repeated in connection with field trials [and clinical trials], than that we must ask Nature few questions, or, ideally, one question at a time. The writer [Fisher] is convinced this view is wholly mistaken. Nature, he suggests, will best respond to a logical and well-thought-out questionnaire. Indeed, if we ask her a single question, she will often refuse to answer until some other topic has been discussed."[24]

Resolving one of the multiplicity issues helps in understanding and potentially solving other issues. Consider dose-response because its solution reveals solutions for other multiplicity issues. Getting the dose right has always been a difficult problem in drug development, and it is an expensive problem—unnecessarily expensive. In AD, identifying the wrong dose in phase 2 likely accounts for many of the failures in phase 3 trials. However, it is difficult to know for sure because it is impossible to distinguish between a phase 3 failure caused by an ineffective dose and one caused by an ineffective drug.

Traditional dose-response clinical trials are woefully inefficient. The conventional approach is to compare doses with placebo in a pairwise fashion and then to pay statistical penalties in type I error rate. Half of the problem is cured by recognizing that the true response for a dose between two other doses is almost always between the true responses at the other doses. Researchers should model the dose-response relationship with a family of functions that allow for monotonicity. Then, if the data are consistent with the assumption of monotonicity, the modeling process borrows outcome information across doses, greatly increasing the power of the trial.

Such modeling applies regardless of how dose assignments are made, even if they stay the same throughout the trial. But it is possible to do a lot better by adapting randomization. That is the other half of the solution. Assigning to some doses will be relatively uninformative about what doses are better. Non-informative doses will be revealed by interim results as the trial proceeds. Researchers should build design algorithms that assign few if any patients to such doses.

Imagine a robot that has been programmed to assign doses to patients—artificial intelligence. The robot is unblinded to accumulating data and "observes" what doses are performing well and which are not. It learns. Program the robot to avoid underperforming doses, including dropping such doses…with the possibility of restarting doses that are becoming more promising with longer follow-up. The robot is very specifically programmed to learn about doses that are likely doses for phase 3, say. Have it stop the trial when it knows enough to make a go/no-go decision regarding phase 3, and when it determines what dose or doses to use in phase 3 if the drug is a "go."

Go/no-go decisions should depend on Bayesian predictive probabilities of a successful phase 3 assuming longer follow-up of patients already enrolled in the trial. Phase 3 can be a second trial or a second stage of the present trial. In the latter case, the trial can shift seamlessly into the second stage with the intention that the combination of the two stages will count as a single phase 3 trial.

Once the robot has modeled dose-response and adapted to results accruing in the trial, it has other important tasks. One involves the endpoint. Suppose the primary endpoint is some combination of cognition and function at 12 months. Earlier information about the patients' responses to treatment may be available (including the same cognition/function measure, just assessed earlier). You, the designer, build a model that has unknown longitudinal parameters for the robot so that it can predict the primary endpoints for those patients who do not yet have 12-month visits. This longitudinal model should depend on treatment arm (ie, dose) as well as patient covariates. Patients with fewer than 12 months follow-up have a probability distribution in place of primary endpoint. Therefore the robot's statistical analyses, including interim analyses, can include all patients accrued so far in the trial via multiple imputation.

Coming this far means you have learned about the lecanemab phase 2 trial 201 in AD [15,25], the Pfizer ASTIN trial in stroke [26], and Eli Lilly's AWARD-5 phase 2/3 trial of dulaglutide in type 2 diabetes[27]. These three trials had some similarities, including that they were wholly Bayesian.

One aspect of the lecanemab trial deserves special mention: modeling missing data. The Bayesian longitudinal model of AD in this phase 2 trial[15] was essential in view of the substantial missing data. Namely, the model applied whether the missingness was due to missing visits or right censoring. Some of the right censoring was caused by an external regulator. In all cases the modeling worked perfectly. The protocol specified Bayesian analysis of the phase 2 trial exactly predicted the outcome of the lecanemab phase 3 trial[15,28].

Finally, Lilly's AWARD-5 trial had three additional jobs in its robot's workload[27]. One was to include safety in the primary analysis via a

clinical utility index (CUI) that would be used for all the robot's decisions. Each of the CUI's components required longitudinal modeling. The second job was making the phase 3 go/no-go decision and picking the two doses that would move seamlessly to a fixed-randomization stage 2 if the decision was "go," which it was. Third, the robot determined the sample size for the fixed-randomization stage 2 (which would be combined with stage 1 dose-finding results in carrying out the trial's final analysis).

The FDA has been enormously supportive of such innovations. Its support includes granting accelerated approval of lecanemab-irmb (Leqembi®) based on phase 2 trial 201 and full approval of the two doses of dulaglutide (Trulicity®) based on the AWARD-5 trial and other phase 3 trials that compared dulaglutide with active control arms. An FDA initiative that may have been affected by these trials is the CID[1].

An FDA initiative of its Oncology Center of Excellence (OCE) called Project Optimus regards getting the dose right[29]. Their guidance dated August 2024 addresses the possibility that two or more doses are carried into a phase 3 trial with the intention of dropping all but one dose during the trial. According to the guidance's Section III, Dosage Optimization Recommendations, subsection B, Trial Designs to Compare Multiple Dosages: "The trial does not need to be powered to demonstrate statistical superiority of a dosage or statistical non-inferiority among the dosages using type I error rates which would be used in registrational trials." So there is no need for statistical significance ($P < 0.05$) of one of the doses over another dose in order to drop the latter for inferiority. An interpretation of this directive is, "Give us some randomized evidence comparing the doses with each other but not necessarily highly powered evidence."

In recognition that there is an impact on a trial's overall type I error rate associated with dropping an arm, the guidance goes on to say that "the trial design should provide strong control of Type I error." Indeed, this and other adaptations are accommodated in the trial simulations to demonstrate control of type I error.

This attitude is enormously important and may set a positive regulatory precedent. The term *moderate power* for adaptive decisions applies to those for which "The trial does not need to be powered to demonstrate statistical superiority … or statistical non-inferiority." It is not clear whether moderate powering applies in other circumstances (such as adaptively dropping single agents in a factorial trial) or for other FDA divisions (such as Neurology). However, in my experience the OCE is serious about moderate powering regarding adaptively dropping doses during registration trials in oncology. In March 2023, the OCE agreed with my proposal to drop one of two doses in an ongoing trial based on a moderate Bayesian probability of inferiority.

Factorial designs

In developing combination therapies, "moderate powering" should be proposed in what the FDA called "adaptive design elements of factorial and partial factorial designs." Consider two drugs, A and B, at least one of which is investigational. Combination AB is compared in a clinical trial with no therapy, A^cB^c, where superscript ^{c} stands for complement. If AB fares significantly better than A^cB^c in the trial, should the combination be approved? No, not unless there's good outside-the-trial evidence that both A and B are contributing to the outcomes of combination AB.

At a July 25, 2024 meeting of an FDA advisory panel, the Oncologic Drugs Advisory Committee (ODAC) was presented results of a trial that had compared AB with A^cB^c. The FDA's briefing document for ODAC stated the FDA's position, including that "in a Type B meeting held on November 01, 2018, FDA stated the design of AEGEAN [the trial in question] would not isolate the effect of the treatment phases [A and B] and recommended that the Applicant should consider a factorial study design, potentially with adaptive design elements. The Applicant opted to proceed with a two-arm trial."

The specifics of AEGEAN were a bit different from what the above description. Therapies A and B were not different drugs but different periods (phases) of using the same drug, neoadjuvant and then adjuvant. So in essence AB was longer therapy, called "perioperative." It can be thought of as a dose regimen. The FDA asked ODAC to vote on this question: "Should FDA require that new trial design proposals for perioperative regimens for resectable NSCLC include adequate within trial assessment of contribution of treatment phase?" ODAC voted "Yes," unanimously.

FDA and ODAC questioned the applicant regarding why they had not conducted a factorial trial. A 2×2 factorial trial would have four treatment groups: AB, AB^c, A^cB, A^cB^c. The applicant's rationale in answering a direct question from ODAC was that a factorial design or even a 3-armed (partial factorial) design would require a much larger sample size and would take much longer to conduct—in their discussion, ODAC used the estimate of two years longer.

As explained below, this response and its rationale misses out on the fundamental benefit of factorial design. My explanation will also suggest what the FDA likely meant by "potential adaptive design elements." Further, it raises the issue of whether "moderate powering" can be applied to factorial designs and other similar innovations.

The applicant's presentation and the ensuing discussion at the ODAC meeting was prefaced by the statistical comparisons being across pairs of the four patient treatment arms. That is not what R.A. Fisher had in mind when he invented factorial designs while working at Rothamsted Experimental Station from 1919 to 1933. In 1935, he wrote the book on factorial designs, *The Design of Experiments*[30]. All 10 editions of the book have stressed that statistical analyses of factorial designs should focus on the factors (main effects) and not on individual arms. The difference is critical, with implications on statistical power and sample sizes.

Consider AB – AB^c and A^cB – A^cB^c. These two differences are independent, and both estimate the benefit of factor B. The best single estimate of that benefit is the average of the two. Similarly, AB – A^cB and AB^c – A^cB^c are independent estimates of factor A. The primary analyses in a classical 2×2 factorial experiment are estimates of the "main effects of A and B" and not, for example, on comparison A^cB versus A^cB^c for the effect of B. A secondary analysis is estimating the interaction between A and B. For example, the two estimates of B's effect, AB – AB^c and A^cB – A^cB^c, may be different. Assuming that there's no interaction means the second factor is included in the trial for free.

Fisher argued that there are two advantages of factorial design. One occurs when there is no interaction because you then get two trials for the price of one. The other occurs when there is an interaction, for in that case, a factorial design is the only way to get information about the interaction. But to repeat, addressing interactions does not require high power.

A reviewer suggested that my enthusiasm for factorial designs may be excessive. One concern was the possibility of ambiguous interactions. Similarly, an NIH cooperative group statistician once told me they had designed a factorial design and it was a disaster; they'd never do it again. So what happened? It turned out that both single agent arms were as effective as their combination; a classical negative interaction. My reaction: "That's great. You learned something very important. Suppose you had run a two-armed trial instead, comparing the combination with control. Think of all the people who would have been overtreated before the error was discovering." There is no outcome that would lead me to regret using a factorial design. There are many outcomes of non-factorial trials that would lead me to regret not using a factorial design, including a case in I-SPY 2.

Example of two trials for the price of one

In the 1990s the breast cancer committee of the Cancer and Leukemia Group B (CALGB), a national oncology group, carried out many trials having factorial designs at my urging. None of these trials suggested even a hint of an interaction either before or after the results

became known.

As an example, in 1993–1994, CALGB was charged by the US. Breast Cancer Intergroup with designing and running the next adjuvant breast cancer trial in lymph node–positive disease. There were two main competing proposals for the scientific question to be addressed. One was to add four 3-week cycles of paclitaxel (Taxol®) to the standard four 3-week cycles of doxorubicin and cyclophosphamide.

The other proposal from the breast cancer community was the dose-response of doxorubicin. The standard dose was 60 mg/m^2. A previous CALGB study had shown that this dose was better than two lower doses. When this trial was being designed in the 1990s, there was a great deal of hype and some negative opinions in the community regarding high-dose therapy. The proposers of this factor wanted to address three doses of doxorubicin: 60, 75, and 90 mg/m^2.

My recommendation was to conduct a 3 × 2 factorial that would address both questions. There had been very little experience with factorial trials in cancer research, and there was some reluctance to undertaking such an innovation. But after several presentations to the CALGB, they agreed. Most important was the strong support of Craig Henderson, MD, the chairperson of the CALGB Breast Cancer Committee. We met with some resistance at the US Breast Cancer Intergroup level. They worried that presenting a complicated trial to patients would affect accrual. Thus, we incorporated the option to drop two of the six treatment arms if the trial did not accrue well, a simple type of adaptation that required no statistical adjustment because it depended only on information about the trial that was openly available.

There was a bottleneck at the sponsoring agency, the National Cancer Institute. Their statisticians expressed concern that the proposed 3000 patients to address the paclitaxel question would not be enough to highly power the ability to address the interaction between paclitaxel and dose of doxorubicin. But they eventually agreed that not all questions in a clinical trial need to be answered with high power. And they agreed that the two factors in this trial were unlikely to interact. Moreover, we had "moderate power" to address interactions, and some information is better than no information.

We ran the trial, CALGB 9344 [31,32]. It accrued surprisingly well, with 3121 patients across the six treatment arms. The trial was practice-changing in two ways, based on the two main effects[32]. Paclitaxel reduced the risk of recurrence or death by 17 %. In 1999 the drug received FDA approval based on CALGB 9344. As regards the other factor, increasing the dose of doxorubicin in the trial showed no difference in clinical outcomes. Further, there was not even a hint of an interaction between the two factors. The results and conclusions were so clear that the dose question and the fact that paclitaxel was only one of the two main effects in a factorial trial were not even mentioned at the ODAC meeting that addressed the approval of adding four cycles of paclitaxel. Both the use of paclitaxel and the doxorubicin dose of 60 mg/m^2 continue to be standard in clinical practice today.

Somewhat serendipitously, the circumstance of CALGB 9344 offered a perfect opportunity to check claims about the benefits of factorial designs. An almost identical trial, B-28 [33], was conducted at the same time by the National Surgical Adjuvant Breast and Bowel Project (NSABP). The difference between the two trials was that B-28 did not have a factorial design. It addressed only the addition of paclitaxel. All patients received the 60-mg/m^2 dose of doxorubicin. The sample size of B-28 was 3060, only 61 patients fewer than CALGB 9344. Moreover, B-28′s outcome was the identical 17 % reduction in disease recurrence associated with adding paclitaxel. Regarding trial length, the time between first patient accrued and announcement of results was essentially the same in the two trials. Thus, the factorial design was truly two trials—two practice-changing trials—for the price of one. And there were no negative consequences of doubling the value of the trial, including essentially no extra cost.

Sizing factorial clinical trials and adaptations

The unfortunate and undeserving reputation of factorial designs regarding increased sample size stems from the tradition of comparing arms rather than main effects. A clinical question is, "What do A and B contribute to the combination AB?" This question cannot be addressed adequately by any two-arm clinical trial. Analyses of factorial designs that ignore the relationships among the four arms are scientifically flawed. They leave critical information on the table.

If one assumes there is no interaction between factors, then there is *no increase in sample size* over a two-armed trial that addresses a single factor. Of course, one should test for interaction at the end of the trial. If there is a suggestion of interaction, then that would be important and useful information.

Adaptive factorial clinical trials

In accordance with moderate powering for an adaptation, a sponsor could begin a clinical trial with a factorial design having equal randomization probabilities to the four arms but then adapt the randomization to the accumulating data. There are many possibilities. For example, suppose the interim results and predictive probabilities of future results are suggesting that factors A and B are both contributing to the benefit of AB. Then, single-agent arms, which in the above notation are arms A^{c}B and AB^c, could be assigned lower probabilities and even eventually dropped completely (but with follow-up continuing for all patients in the trial). The two arms remaining would be AB and A^{c}B^c, which would maximize the precision regarding the combination versus no therapy. In any case, the sample sizes for the individual arms should depend on predictions of the future of the trial with potential effects on sample sizes. The final sample size will be random, but as the FDA suggested at the aforementioned ODAC meeting, it would almost certainly be substantially smaller and the trial substantially shorter than the sample sizes that were presented by the applicant and that were cited by the ODAC panel members.

There are various adaptations to consider. A tack that is an opposite of that in the previous paragraph also works. Emphasize AB and A^{c}B^c early in the trial, dropping or lowering its randomization probability when there is substantial predictive probability that the trial will demonstrate a benefit for AB over A^{c}B^c. The primary focus of the trial would then switch to isolating the contributions of both A and B to AB. Regardless of tack, the design algorithm can be built to decide which if any of the candidate therapies are better than which other therapies.

All adaptations must be set in stone prospectively and applied in accordance with the trial's protocol and Statistical Analysis plan (SAP). Prospective design is necessary to enable what the FDA calls "strong control of type I error" for the primary final analyses. Calculating and controlling Type I error rate will no doubt require simulation. Such a trial could qualify for FDA's CID initiative as a registration trial[1].

5. Discussion and conclusions

In the spirit of R.A. Fisher, it is always possible and it is always efficient to ask more than one question in a clinical trial. Adaptive factorial designs are always available in trials that address combination therapies. Sometimes, as in the case of interactions in factorial trials, achieving efficiency requires modeling and making assumptions and perhaps synthesizing with evidence from outside the trial in question. For NIH and patient advocacy-sponsored trials there is no excuse for running one-question clinical trials. On the other hand, industry-sponsored drug trials will no doubt continue to be predominately two-armed trials. However, industry trials addressing combination therapy should use adaptive factorial trials as described above.

The Bayesian approach has always had theoretical appeal—see Table 1. Over the past 30 years, the theory has been applied in designing actual clinical trials. Bayesian trials still represent a small minority of all

trials, but their existence is changing the way investigators, regulators, and government and industry sponsors view innovation in clinical trials.

By far the most important Bayesian contribution to clinical trials is the ability to observe the accumulating results and modify the future course of the trial on their bases. The approach in this article is that the "observer" is an automaton armed with a prospective algorithm that spells out and dictates adaptations that were determined in advance of the trial. Any such design can then be simulated to calculate its type I error rate and statistical power.

The Bayesian adaptive approach applies to addressing and answering multiple questions in a single clinical trial. An example includes evaluating many doses. Another is evaluating the effectiveness of combination therapy versus single-agent therapies while also considering questions regarding which therapies are best in which patient biomarker-defined subpopulations.

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Special Article

Risk reduction and precision prevention across the Alzheimer's disease continuum: a systematic review of clinical trials combining multidomain lifestyle interventions and pharmacological or nutraceutical approaches

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Randomized controlled trial

ABSTRACT

To effectively combat dementia onset and progression, lifestyle-based interventions targeting multiple risk factors and disease mechanisms through a multidomain approach - tailored and implemented early in the disease process - have emerged as promising. Electronic databases and relevant websites (clinicaltrials.gov, euclinicaltrials.eu, PubMed and EMBASE) were systematically searched for randomized controlled trials (RCTs) testing the combination of multidomain lifestyle and pharmacological interventions. Studies were included if 1) lifestyle intervention was multimodal (≥2 domains); 2) it was combined with drugs, supplements, or medical food; 3) the study population was within the Alzheimer's disease (AD) and related dementias continuum, including cognitively normal individuals at-risk for dementia, people with subjective cognitive decline (SCD), mild cognitive impairment (MCI), or prodromal AD; 4) outcomes included cognitive or dementia-related measure(s), and 5) intervention lasted at least 6 months. Twelve combination RCTs were identified, incorporating 2 to 7 lifestyle domains (physical exercise, cognitive training, dietary guidance, social activities, sleep hygiene, cardiovascular/metabolic risk management, psychoeducation or stress management), combined with pharmacological components (e.g., Omega-3, Tramiprosate, vitamin D, BBH-1001, epigallocatechin gallate, Souvenaid, and metformin). Seven RCTs targeted participants with prodromal AD, MCI or early dementia, five focused on at risk individuals or SCD. Additionally, 2 studies adopted a precision medicine approach by enriching populations with *APOE-ε4* carriers. Findings suggest that well-designed interventions - tailored to the right individuals, implemented at the optimal time - may effectively improve cognition. However, further refinement of the RCT methodology is warranted, for better alignment with the multifaceted nature of dementia prevention and management.

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1. Introduction

Healthy ageing, preservation of cognitive functioning, and preventing Alzheimer's disease (AD) and related dementias (ADRD) is a global priority, as effective ADRD therapeutics are still not widely available. Efforts to find effective treatments are focused on identifying new compounds as well as drug repositioning and repurposing that may potentially delay the onset, slow disease progression, or, ultimately, prevent dementia [1]. Despite recent promising results from anti-amyloid β monoclonal antibody[2,3] therapies with Lecanemab and Donanemab showing potential in slowing cognitive decline, current estimates indicate that <30 % of AD patients would be eligible for these therapies [4,5]. Additionally, the failure of numerous pharmacological and non-pharmacological single-domain interventions in AD underscores the limitations of targeting single-disease mechanisms or single risk factors. There is a clear need for strategies addressing multiple risk factors and biological pathways simultaneously, with early intervention in the ADRD continuum being crucial for an optimal preventive effect [6,7]. These new multidomain therapeutic approaches could enhance treatment efficacy and personalize prevention efforts.

Recently, the update of the Lancet Commission on Dementia Prevention, Intervention and Care included 14 modifiable risk factors for dementia (mostly based on observational studies): low education, hearing and vision loss, traumatic brain injury, hypertension, excessive alcohol use, obesity, smoking, depression, social isolation, physical inactivity, air pollution, diabetes, and high level of low-density lipoprotein (LDL) cholesterol levels [8]. Modifying these factors could prevent or delay up to 45 % of dementia cases. The World Health Organization (WHO) guidelines for risk reduction of cognitive decline and dementia, which are based on the synthesis of findings from intervention trials, recommend, among others, physical activity, a healthy balanced diet, cognitive training, as well as management of hypertension, diabetes, and dyslipidemia, for reducing the risk of cognitive decline [9]. The WHO guidelines are currently being updated, and the new edition will include the addition of new modifiable lifestyle factors and multidomain interventions.

Multidomain lifestyle interventions, e.g., based on the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), reported promising cognitive benefits in older individuals at risk of dementia including[10] in those with genetic susceptibility (*APOE-ε4* carriers) [11,12]. The FINGER randomized controlled trial (RCT) combined 5 components - exercise, cognitive training, social engagement, dietary recommendations and vascular/metabolic risk factor management - in a 2-year intervention [10]. The FINGER study is now a model for similar trials around the globe, with the World-Wide FINGERS (WW-FINGERS) network including 70 member countries and offering a new paradigm to prevent cognitive decline [13].

Given the growing number of modifiable risk factors being identified for late-life dementia, there is a growing need for novel multidomain combination trials. Integrating multidomain lifestyle interventions with pharmacological treatments - whether novel or repurposed - holds promise for advancing precision medicine approaches aimed at preventing cognitive decline and dementia. Existing strategies for cardiovascular and cancer treatment offer useful models for testing combination therapies in ADRD RCTs [7,14].

Over the past decade, combination trials in the ADRD field have been initiated, focusing on combinations of multidomain non-pharmacological lifestyle interventions and pharmacological compounds [15–17]. In this context, we conducted a systematic review to provide a comprehensive overview of such combination RCTs. The review focused on key methodological aspects, such as intervention and trial design, target populations, intervention duration, and adherence. Our aim is to inform the design of future combination RCTs, by identifying common pitfalls and exploring how current and emerging evidence can be leveraged to optimize trial design and guide the development of more effective intervention strategies.

2. Methods

2.1. Search strategy

We followed the Preferred Reporting Items for Systematic reviews and Meta Analyses (PRISMA) 2020 guidelines [18]. To identify combination therapy RCTs, records in Clinicaltrials.gov and euclinicaltrials.eu databases were searched with the following terms: "Alzheimer`s disease, " "mild cognitive impairment," "dementia," "cognitive decline," combined with either "lifestyle intervention," "multidomain," or "multimodal" from inception to May 30, 2025. PubMed and EMBASE were also searched with the same combination of terms in case of omission. All searches were performed independently by E.B. and P.P.

2.2. PICO components and inclusion and exclusion criteria

Based on the Population/Intervention/Comparator/Outcomes (PICO) components, the review aimed to identify RCTs targeting adults with normal cognition, or subjective cognitive decline (SCD) or mild cognitive impairment (MCI) or prodromal AD (P); testing lifestyle-based interventions that addressed at least 2 modifiable risk factors for dementia, or included at least 2 intervention components, in combination with additional treatments, such as pharmacological (i.e., drugs), nutraceutical (e.g., medical food, dietary supplements) or the use of non-invasive devices (e.g., transcranial brain stimulation) (I); included appropriate comparators such as placebo, standard of care, lower intensity intervention (C); and assessed the intervention effect on outcomes related to dementia and cognitive impairment (O). RCTs were included regardless of their current status (ongoing, completed, terminated, unknown), or whether published results were available. We excluded RCTs with interventions/treatments that lasted less than 6 months. Studies were also excluded if they included participants with a suspected or known dementia diagnosis, other major neurological or psychiatric disorders (e.g., Parkinson's disease, stroke; major depression, multiple sclerosis, schizophrenia, bipolar disorder), history of substance abuse, as well as studies focusing on rehabilitation programs for recent cardiovascular, cerebrovascular, respiratory or other medical events, e.g., post-surgery. The search was not limited by date of publication nor geographical location; however, only records or publications in English were included.

2.3. Study selection

The Covidence systematic review software was used to manage search results from clinicaltrials.gov, PubMed, and EMBASE. Those derived from euclinicaltrials.eu were manually checked. After duplicates were removed, Title and Abstracts were screened independently by 2 researchers (E.B. and P.P.). The full texts of potentially eligible studies were then obtained and further assessed. Any disagreement on inclusion was resolved by consensus within the research team.

2.4. Data extraction

Eligible RCTs had the following data extracted: National Clinical Trial (NCT) number, study title, acronym of the study, current status, number of trial arms, drug component, dose, lifestyle intervention domains, the intervention intensity or modality, primary outcomes, secondary outcomes, trial duration, age for study inclusion, study population (AD continuum), trial sample size, trial timeframe, masking, trial phase, sponsor, and number of sites and countries.

3. Results

3.1. Characteristics of the multidomain combination RCTs

Following our search strategy, 1352 RCTs and 7087 publications were initially identified. After removing duplicates, 2039 publications were screened to assess combinations of lifestyle interventions with pharmacological, nutraceutical or other treatments. This screening process resulted in the identification of 12 combination RCTs (as of 2025.05.30, Fig. 1, Table 1), using several classes of compounds combined with multidomain lifestyle interventions, targeting individuals within the continuum of AD and dementia risk. This included people with normal cognition but increased dementia risk due to risk factors that were not well controlled, identified via validated scores, and people with a diagnosis of SCD, or MCI (defined via different set of diagnostic criteria)[19–21] or prodromal AD. Two RCTs included both MCI and early stage dementia. For some RCTs, participants' inclusion relied on cognitive screening and assessment of modifiable risk factors (e.g., MET-FINGER, Multidomain Alzheimer Preventive Trial, or MAPT) [15, 22]. One trial specifically included participants with MCI who also had concomitant type 2 diabetes (T2D) or insulin resistance, while 2 studies adopted a precision medicine approach by enriching their study populations with individuals carrying the *APOE-ε4* allele (Table 1).

3.2. Duration, frequency and types of intervention domains

A total of 4434 participants were included in the eligible RCTs, with the number of participants ranging from 35 to 1680 (Table 1), and intervention length ranging from 6 to 36 months. Two RCTs had been terminated early as a consequence of the SARS-CoV-2 pandemic (IRMCI and SYNERGIC). Seven RCTs had 2 arms, two RCTs had either 3 or 4 arms, while 1 RCT featured 5 study arms (Table 1). Two studies opted for quadruple masking (P—participants, CG—caregiver, I—investigator, OA—outcome assessor), 3 for triple masking (P, OA, and either I or CG), 2 for double masking (P, OA), 4 studies for single masking (P or OA), and 1 trial opted for an open label approach. Earlier trials incorporated 2 to 3 intervention domains, typically combining physical exercise with either cognitive training or dietary guidance. Later studies expanded their multidomain approaches, integrating further domains such as social engagement, cardiovascular risk management, meditation, or sleep hygiene education. Physical exercise emerged as the most frequently utilized component of intervention, present in all 12 RCTs, with most studies utilizing moderate-to-high intensity progressive training approaches, and only 1 RCT opted for low intensity (Table 1). Ten RCTs incorporated cognitive training in their intervention domains with varying intensities and frequency along with dietary guidance varying between Mediterranean-like and a ketogenic diet, through general healthy dietary advice. Five RCTs incorporated guidance on social activities, ranging from suggestions such as dancing or participating in

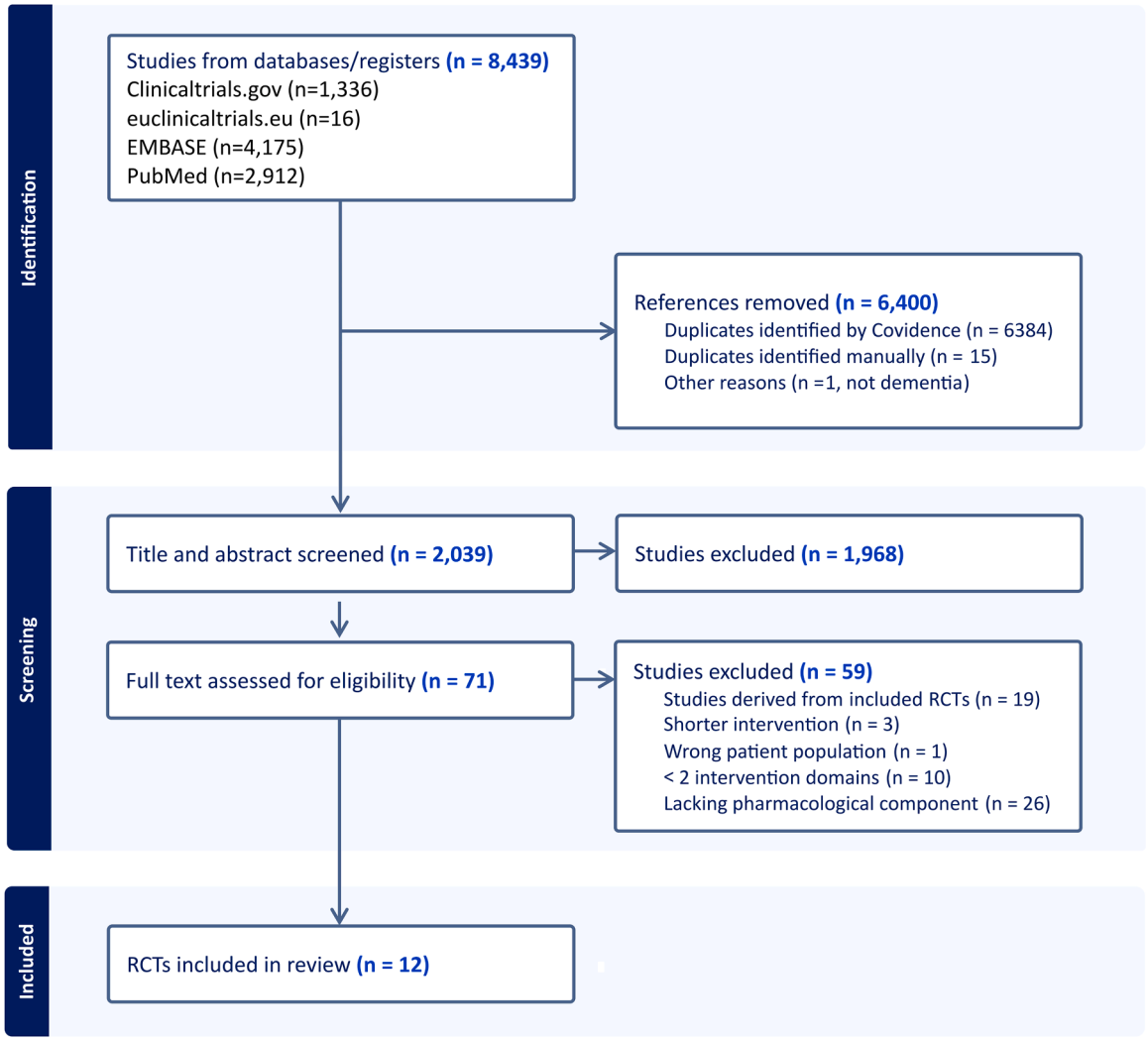

Fig. 1. Flow diagram of RCT screening and selection process.

Table 1
Clinical trials of multidomain lifestyle interventions combined with pharmacological compounds. RCTs are organized in chronological order. Abbreviations: AD, Alzheimer`s disease; ADAS-Cog, Alzheimer's Disease Assessment Scale Cognitive; ADCS-PACC, Alzheimer's Disease Cooperative Study—Preclinical Alzheimer Cognitive Composite; A-IADLQ, Amsterdam Instrumental Activity of Daily Living Questionnaire; AQ, Alzheimer's Questionnaire; BB, Blood based; CDR, Clinical Dementia Rating; CG, Caregiver; CT, cognitive training; Cv, cardiovascular; D, diet; EGCG, Epigallocatechin gallate, EQ-5D-5L, Euro Quality of Lif—5 dimensions- 5 levels; I, Investigator; LIBRA, Lifestyle for Brain health; M, Meditation; MCI, Mild cognitive impairment; MMSE, Mini mental State Examination; MoCA, Montreal Cognitive Assessment; MRI, Magnetic Resonance Imaging; NA, Not applicable; NTB, Neuropsychological Test Battery; OA, Outcomes assessor; P, Participant; PE, Physical exercise; PsE, Psychoeducation; PROMIS, Patient-reported Outcome Measurement Information System; RAVLT, Rey Auditory Verbal Learning Test; S, Stress management; SA, Social activities; SCWT, Stroop color and word test; SH, Sleep hygiene; SCD, Subjective cognitive decline; T2D, type 2 diabetes; TMT, trail making test. Unless specified, the intervention is delivered by in-person activities, with some RCTs doing intermediate follow-ups also via phone. Trial timeframe covers the entire period from study initiation to completion including recruitment and intervention phases.

CT Number	Study Title	Acronym	Study status	Trial Arms	Drug Component	Dose	Lifestyle Intervention	Intervention/ Intensity Modality	Primary Outcome	Secondary Outcome	Duration	Age	Population	Trial Size estimated	Trial Timeframe	Masking	Phase	Sponsor	Nr sites/ Nr Countries
CT00672685	Omega-3 Fatty Acids and/or Multi-domain Intervention in the Prevention of Age-related Cognitive Decline	MAPT	Completed	4	Omega-3	800 mg DHA + 225 mg EPA/day	PE, CT, D, Cv	Moderate/group sessions	Change in global cognitive composite Z score: free and Cued Selective Reminding test, MMSE-10, DSST (Wechsler AIS), Category naming test	Components of cognitive tests, ADCS-ADL PI, SPPB, Fried's frailty criteria, CDR-SB, GDS-15, adherence to multidomain intervention	36 mo	>70 y	SCD or limitation in one instrumental activity of daily living, or slow gait speed	1680	2008.05-2014.04	Triple (P, I, OA)	3	University Hospital, Toulouse, France	13/2
NCT01219244*	Effects of Dietary Interventions on the Brain in Mild Cognitive Impairment (MCI)		Completed	2	Omega-3 plus Vitamin E	2200 mg/day (1320 EPA+880 mg DHA)+ 15 mg Vitamin E	PE, CT	Moderate high/gradually increasing/group + individual sessions	Change in cognitive function domains by the Neuropsychological test battery (German version of the AVLT, forward and backward digit spans, verbal fluency (semantic and phonemic), TMT part A and B, and STROOP Color-Word test	MRI, BMI, Body Fat, lipid profile, Vit. B12, Folate HBA1c, insulin, leptin, IL-6 etc.	6 mo	60-80 y	MCI	35 (within a larger project expected to recruit a total of 330)	2010.08-2016.07	Quadruple (P, CG, I, OA)	2/3	Charite University, Berlin, Germany	2/1
NCT02409238	Insulin Resistance and Mild Cognitive Impairment (IRMCI) Study	IRMCI	Terminated	2	Metformin	750 mg/day	PE, D	Moderate/not specified	Change in cerebral glucose metabolic rate (FDG-PET/MRI), change in composite Z score of cognitive battery	Components of cognitive tests, ADL, Cog-IADL, CDR-SB, MMSE, MoCA, fasting plasma insulin, HbA1c, BMI, lipid profile, etc.	24 mo	>55 y	MCI (T2D or prediabetes)	360 (actual 105)	2015.03-2019.12	None	4	SingHealth Polyclinics, Singapore	1/1
NCT03382353	EMuNI Project: Multiple Nonpharmacological Interventions	EMuNI	Completed	3	Tramiprosate	100 mg/day	PE, CT, D	Moderate/group + Individual + online sessions	Change in cognitive function assessed by RAVLT and composite score of neuropsychological tests	MRI-structural, DTI	12 mo	60-80 y	SCD	120 (actual 134)	2016.01-2018.06	Single (OA)	NA	IRCCS Centro San Giovanni di Dio Fatebenefratelli, Italy	2/1

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Table 1 (*continued*)

CT02741804	Lifestyle Intervention Program for Cognitive Impairment		Unknown	2	BBH-1001	Turmeric 125 mg, fisetin 16.65 mg, green tea leaf extract 17.5 mg, EPA 75 mg, DHA 150 mg, Vitamin D3 250IU/day	PE, CT, D, M, SA, SH	Low/not specified	Change in retinal amyloid burden (measured by retinal scan)	NTB, MRI, FDG-PET, incidence of dementia, BB markers, glucose and HbA1c, vascular risk factors	18 mo	>55 y	MCI	150	2016.05-2019.05	Single (P)	NA	Cedars-Sinai Medical Center, USA	1/1
NCT02808676	SYNchronizing Exercises, Remedies in Galt and Cognition	SYNERGIC	Terminated	5	Vitamin D3	10.000 IU (3x/week)	PE, CT	Moderate high, gradually increasing/group sessions	Change in cognitive function assessed by ADAS-Cog 13, ADAS-Cog plus	Cognitive test components, gait and mobility performance,	6 mo (+6 mo post-intervention follow-up)	60-85 y	MCI	200 (actual 175)	2016.07-2020.11	Double (P, OA)	NA	Lawson Health Research Institute, Canada	5/1
NCT03249688	Multimodal Preventive Trial for Alzheimer's Disease	MIND-AD$_{mini}$	Completed	3	Souvenaid	125 mL/day (omega-3, uridine mono-phosphate, choline, vitamin B12, B6, C, E, folic acid, phospholipids, selenium)	PE, CT, D, Cv, SA	Moderate high, gradually increasing/group+ individual sessions	Feasibility (recruitment rate, retention rate and adherence)	Adherence to intervention domains, adherence to healthy lifestyle changes, healthy dietary intake, physical, cognitive and social activities, overall cardiovascular risk burden, etc.	6 mo (+6 mo post-intervention follow-up in Sweden)	60-85 y	Prodromal AD	150 (actual 93)	2017.10-2019.12	Double (P, OA)	NA	Karolinska Institutet, Sweden	4/4
NCT04606420	Can Lifestyle Changes Reverse Early-Stage Alzheimer's Disease		First 20 w intervention completed	2	Multinutrient supplements	Multiple	PE, D, S	Moderate/not specified	Change in cognition and function assessed by ADAS-Cog, CGIC, CDR-SB, CDR Global	BB markers (eg, plasma Aß42/40 ratio), microbiome taxa	20 w, followed by 20 w with cross-over only for control group	45-90 y	MCI, early stage dementia	100 (actual 51)	2018.09-2023-09	Single (OA)	NA	Preventive Medicine Research Institute, USA	4/1

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Table 1 (*continued*)

NCT03978052	Prevention of Cognitive Decline in ApoE4 Carriers With Subjective Cognitive Decline After EGCG and a Multimodal Intervention	PENSA	Completed	2	EGCG	300 or 500 mg (based on body weight)	PE, CT, D, PsE, SA	Moderate high/gradually increasing/group + individual + online sessions	Change in global cognition by composite measure of modified ADCS-PACC, to include tests of executive function (PACC-exe)	Change in brain connectivity (fMRI and structural MRI), treatment safety and tolerability	12 mo (+ 3 mo post-intervention follow-up)	60-80 y	SCD and ApoE-ε4 carriers	200 (actual 129)	2019.10-2023.03	Double (P, OA)	NA	Parc de Salut Mar, Spain	2/1
NCT05256199	Dutch Multidomain Lifestyle Intervention in Older Adults at Risk of Cognitive Decline	FINGER-NL	Ongoing	2	Souvenaid	125 mL/day (omega-3, uridine mono-phosphate, choline, vitamin B12, B6, C, E, folic acid, phospholipids, selenium)	PE, CT, D, Cv, SA, SH, S	Moderate high, gradually increasing/group + individual + online sessions	Change in global cognitive composite score assessed with the NTB	Change in individual cognitive tests, A-IADL-Q, Euro-QoL-5D-5L, LIBRA, and intervention domain specific outcomes (e.g. SQUASH, sedentary behavior, sarcopenia, CV risk factors, lipid profile, BB markers, stress management, perceived social support)	24 mo	60-79 y	At risk of dementia (modifiable risk factors plus either SCD or first-degree family history of dementia)	1210	2022.02-20-ongoing	Double (P, OA)	NA	Alzheimerzentrum Amsterdam, The Netherlands	5/1

* NCT01219244: this study included different dietary interventions (caloric restriction, omega-3 supplementation, resveratrol supplementation) initially tested in single-domain studies, followed by a second step with a combination study including the dietary intervention judged as the most effective, plus physical activity and cognitive training.
** NCT05109169: in this study participants are randomized 1:1 into self-guided (control) vs. structured multimodal lifestyle intervention groups (SMLI). Within the SMLI group, participants who qualify for metformin treatment (elevated adiposity or impaired fasting glucose, but no diabetes) are further randomized 1:1:1 into metformin (2000 mg/day or 1000 mg/day) vs placebo (trial-within-trial).

church events to integrating social engagement within physical exercise or cognitive training domains. Six RCTs employed a combination of individual and group sessions for intervention domains (Table 1, e.g., dietary guidance, physical exercise, and cognitive training) using personalized sessions to tailor the intervention (e.g., addressing weight loss or malnutrition) and group formats to foster socialization and peer support. In contrast, 2 trials relied solely on group sessions (excluding the individually tailored home-based exercises commonly included across studies), while 3 RCTs did not specify how the interventions were delivered. Four trials explicitly targeted cardiovascular or metabolic risk factor management as a distinct intervention domain, while 3 included advice on sleep hygiene, stress management, or meditation. Few RCTs (eg, MET-FINGER, MAPT, MIND-AD$_{mini}$)[17,22,23] specified that the different intervention components were gradually introduced, to facilitate adherence, while this information is not reported for other trials. The transition toward targeting multiple risk factors through multidomain interventions reflects a growing emphasis on comprehensive, data-driven strategies to enhance cognitive health outcomes.

3.3. Outcome measures

The heterogeneity of the interventions and the varying designs across the RCTs, including target groups and outcome measures, provided limited possibility to synthetize the outcomes of RCTs. Thus, a narrative synthesis was chosen to describe the results. Apart from the Multimodal Preventive Trial for Alzheimer's Disease (MIND-AD$_{mini}$), which was a feasibility trial, and the Lifestyle Intervention Program for Cognitive Impairment RCT, where change in retinal amyloid burden was the main outcome, all RCTs had changes in cognitive measures as their primary outcome. Cognitive assessment tools ranged from various validated rating scales to composite scores commonly used in clinical practices such as the Alzheimer's Disease Assessment Scale - Cognitive (ADAS-Cog), the Neuropsychological Test Battery (NTB), the Clinical Dementia Rating scale (CDR), the Montreal Cognitive Assessment (MoCA), the Mini Mental State Examination (MMSE), the Alzheimer Disease Cooperative Study Preclinical Alzheimer Cognitive Composite (ADCS-PACC), the Rey Auditory Verbal Learning Test (RAVLT), or the Stroop color and word test (SCWT). Despite variability in these cognitive assessment tools, core domains such as memory, attention, language, executive function, processing speed and orientation were consistently evaluated, offering a comprehensive view of cognitive function in individuals at risk for dementia. In addition to cognitive outcomes, structural and functional neuroimaging, blood-based biomarkers, and changes in lifestyle indices were often employed as secondary outcome measures, providing a multidimensional evaluation of intervention effects.

3.4. Multidomain lifestyle interventions combined with nutraceuticals

3.4.1. Lifestyle interventions with Omega-3 polyunsaturated fatty acids

Omega-3 polyunsaturated fatty acids (PUFA) have been tested in RCTs with cognitive endpoints in older individuals with or without established dementia diagnosis [24–27]. For some studies, findings pointed towards beneficial effects on cognitive outcomes (visuospatial learning, episodic memory, verbal recognition) in younger-old individuals with age-related cognitive decline (>55 years)[24]; however, no cognitive improvements were found either after shorter (6 months) [26] or longer (24 months)[26] supplementation of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) in cognitively healthy older adults (>65 years, or >70 years respectively). A recent meta-analysis included 24 trials, with 9660 participants, ranging from cognitively normal to MCI. The studies varied in intervention length (3 to 36 months), and in PUFA supplement composition and dosage. Overall, the intake of omega-3 polyunsaturated fatty acids was not associated with significant cognitive changes [28]. However, the existing methodological heterogeneity among studies might prevent proper assessment of the efficacy of omega-3 supplementation, in people with and without cognitive symptoms [28,29].

Supplementation with omega-3 polyunsaturated fatty acids was among the first combination trials conducted, possibly due to their excellent safety, ease of administration and high combination potential with multiple domains of lifestyle intervention [15,30]. The Multidomain Alzheimer Preventive Trial (MAPT, clinicaltrials.gov registration nr: NCT00672685) was the largest 4-arm superiority combination, phase III RCT, including 1680 participants, 70 years and older, with subjective cognitive complaints. Participants were randomized to 1 of 4 groups: lifestyle intervention (physical activity advice, cognitive training, and nutritional consultations) + omega-3 supplementation (daily dose of 800mg DHA and 250mg EPA), lifestyle intervention + placebo, lifestyle control (information sessions on lifestyle) + omega-3 supplementation, or lifestyle control + placebo (Table 1). Primary efficacy outcome was change in the composite *Z* score calculated from the combination of the Free and Cued Selective Reminding Test, 10 MMSE orientation items, the Digit Symbol Substitution Test score from the Wechsler Adult Intelligence Scale, and the Category naming test [15]. Although no significant intervention effect on the primary outcome was reported, positive results were found in sub-group and post-hoc analyses, particularly in individuals with higher dementia risk (increased Cardiovascular Risk Factors, Aging, and Incidence of Dementia, or CAIDE dementia risk score), and in participants classified as amyloid-β–positive via brain PET scan with florbetapir. Cognitive benefits were also seen when pooling all participants who received the multidomain intervention (Table 2) [31].

A smaller RCT enrolling 45 MCI patients (a substudy within a larger study, clinicaltrials.gov ID NCT01219244) has also assessed the combined effect of lifestyle intervention (physical and cognitive domains) with omega-3 supplementation (daily dose of 880mg DHA and 1320 mg EPA supplemented with 15mg vitamin E) [30]. Participants were assessed over 6 months (Table 1). Changes in composite *z* scores of executive function, memory, sensorimotor speed, and attention (based on Auditory Verbal learning test, forward and backward digit spans, verbal fluency, trail making test part A and B, Stroop Color-Word test) were assessed, with no significant differences among the study arms. This pilot study found significantly reduced atrophy in frontal, parietal, and cingulate cortices following combined intervention compared with the control arm (i.e., omega-3 fatty acid supplementation and non-aerobic exercise, Table 2).

While no significant changes were found in cognitive performances after a 6-month[30] or a 36-month-intervention[15] with omega-3 fatty acids combined with multidomain lifestyle intervention, these trials have provided important knowledge on the need to establish the right window of opportunity for such interventions, the right target populations, as well as determination of the optimal dose and treatment duration.

3.4.2. Lifestyle intervention combined with BBH-1001

BBH-1001 is a brain health supplement containing a combination of various nutrients: turmeric (125mg), fisetin (16.65mg), green tea leaf extract (17.5mg), EPA (75mg), DHA (150mg) and vitamin D3 (250IU). Fisetin, a naturally occurring flavonoid with senolytic activity, present in various fruits, vegetables, and teas,[32] has been used alone or in combination in several clinical trials targeting a variety of conditions. The impact of this micronutrient supplement combined with a comprehensive low-intensity lifestyle intervention program was tested on retinal amyloid levels in patients with MCI (NCT02741804, Table 1). Cognitive functioning was assessed as a secondary outcome (change in NTB scores). Participants of this 18-month single-masked 2-arm trial received the BBH-1001 supplement (4 softgels per day) combined with lectures on 6 lifestyle domains (nutrition, physical activity, meditation, sleep hygiene, cognitive activity, and social engagement). The status of this trial is currently unknown, and no published results have been identified.

Table 2
Short summary of published results regarding outcomes from the identified RCTs. Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale Cognitive; ADCS-PACC, Alzheimer's Disease Cooperative Study—Preclinical Alzheimer Cognitive Composite; CAIDE, Cardiovascular Risk Factors, Aging and Dementia; CDR- SOB, Clinical Dementia Rating Sum of Boxes; CGIC, Clinical Global Impression of Change; CI, Confidence interval; CT, Cognitive training; Cv, Cardiovascular; D, diet; EGCG, Epigallocatechin gallate, FDR: false discovery rate; HDI- Healthy Diet Indicator; LDL, Low density lipoprotein; LIBRA, Lifestyle for Brain health; M, Meditation; MCI, Mild cognitive impairment; MEDAS, Mediterranean Diet Adherence Screener; MMSE, Mini mental State Examination; MRI, Magnetic resonance imaging; PE, Physical exercise; PsE, Psychoeducation; S, Stress management; SA, Social activities; SH, Sleep hygiene; Vit, Vitamin.

NCT number	Study Acronym	Intervention (lifestyle plus treatment arm)	Results on primary outcome	Results on other outcomes	Refs
NCT00672685	MAPT	PE, CT, D, Cv + Omega3	No intervention effect on the primary (cognitive) outcomes	•Less decline in 10 MMSE orientation items in lifestyle+ nutraceutical supplement arm versus placebo arm (adjusted p = .036) •In the amyloid β positive sub-population, there was a trend for the combined intervention benefit on the change in composite cognitive score at 12 (adjusted p = .1144, 95 % CI = [0.0136 to 0.3699]) and 36 months (adjusted p = .0690 95 % CI = [0.0190 to 0.5446]) • The combined intervention group showed reduced cognitive decline, compared to placebo, among participants with a baseline CAIDE score ≥6 (p=.023)	[15, 31]
NCT01219244		PE, CT + Omega3-VitE	No intervention effect on the primary (cognitive) outcomes	•Reduced atrophy in frontal, parietal and cingulate cortices of MCI patients following combined lifestyle+ nutraceutical intervention •No changes in inflammatory, metabolic or vascular parameters	[30]
NCT02409238	IRMCI	PE, D + Metformin	NA	NA	
NCT03382353	EMuNI	PE, CT, D + Tramiprosate	•Multidomain intervention + Tramiprosate improved on attention-executive composite score, compared to control arm (p = .002). •No significant differences in other cognitive endpoints	•No significant effects on MRI structural measures, but improvement in functional connectivity of the fronto-parietal executive network in the multidomain intervention, compared to the other arms. • Beneficial effects for the multidomain intervention, compared to control, for depressive symptoms (p = .011), and sled-reported memory complaints (p = .013).	[58]
NCT02741804		PE, CT, D, M, SA, SH +BBH-1001	NA	NA	
NCT02808676	SYNERGIC	PE, CT +Vit D3	•At 6 months, all active arms with aerobic-resistance exercise, regardless of the addition of cognitive training or vitamin D, improved ADAS-Cog-13 when compared with control. Compared with exercise alone, exercise and cognitive training improved the ADASCog-13. No significant improvement was found with vitamin D. The multidomain intervention (exercise + cognitive training + vit D) improved the ADAS-Cog-13 compared with control. •ADAS-Cog-Plus was not modified by any combination of interventions.	•No significant correlations between change in functional brain connectivity and change in cognitive or physical function. •Some significant differences in specific cognitive subdomain tests observed between intervention arms and control group.	[37, 38]
NCT03249688	MIND-AD$_{mini}$	PE, CT, D, Cv, SA + Souvenaid	•In the lifestyle intervention arm, 78.1 % adhered to at least 2 out of 4 intervention domains (attending ≥40 % of sessions) • In the lifestyle + medical food group 87.1 % of participants were overall adherent in 2 out of 4 lifestyle interventions (consuming ≥60 % medical food)	•Good adherence to healthy lifestyle and improved dietary indexes in the intervention + medical food group (HDI: p < .042 and MEDAS: p < .007) compared to control group •The lifestyle + medical food intervention arm had a significantly lower likelihood for decreasing cognitive-functional level (ie, increasing CDR-SOB) compared with control group •No statistically significant differences between either intervention arm or control in global CDR score	[44, 77]
NCT04606420		PE, D, S+ Multi-nutrient supplement	•Significant differences between the intervention group and the control group in cognition and function in the CGIC (p = .001), CDR-SB (p = .032), and CDR Global (p = .037) tests • Borderline significance in the ADAS-Cog test (p = .053)	•Plasma Aβ42/40 ratio significantly differed between intervention and control group (p= 0.003) •LDL-cholesterol decreased in the intervention group, and changes correlated with lifestyle index at 20 weeks (p < .0001, correlation: 0.678) •Significant change in microbiome taxa composition	[60]
NCT03978052	PENSA	PE, CT, D, PsE, SA + EGCG	No intervention effect on the primary (cognitive) outcome	• Significant cognitive benefits assessed by the PACC-exe Z score (P=.005), the Memory Composite Z score (p=.022) and the Semantic Fluency Test (p=.007) were found in the lifestyle+ EGCG group after 15 months (three-month washout period) when compared to participants receiving lifestyle+ placebo intervention. • Both structured lifestyle intervention groups showed significant reductions in LIBRA index	[51]

(*continued on next page*)

Table 2 (*continued*)

NCT number	Study Acronym	Intervention (lifestyle plus treatment arm)	Results on primary outcome	Results on other outcomes	Refs
				scores relative to the control group (lifestyle+EGCG: p =.012; lifestyle+placebo: p =.049) • EGCG supplementation did not affect brain structure nor blood AD biomarkers when compared to placebo • Lifestyle+EGCG group outperformed lifestyle+placebo in improvements in adherence to Mediterranean diet (p=.017) following a three-month washout period.	
NCT05256199	FINGER-NL	PE, CT, D, Cv, SA, SH, S+ Souvenaid	Ongoing	Ongoing	
NCT05109169	MET-FINGER	PE, CT, D, Cv, SA+ Metformin	Ongoing	Ongoing	
NCT05894954	EVANTHEA	PE, CT, D, SH, S+ Personalized intervention	Ongoing	Ongoing	

3.4.3. *Lifestyle intervention combined with vitamin D*

Vitamin D is involved in the regulation of calcium and phosphorus metabolism, with growing evidence suggesting it also exerts neuroprotective effects via antioxidative mechanisms while also inhibiting neuroinflammation [33]. Vitamin D deficiency has been previously associated with alteration in cognitive processes and dementia in preclinical and some clinical studies [33,34]. Over 10 clinical trials in individuals with cognitive impairment have been completed so far, with several still ongoing, testing the effects of vitamin D alone or in combination with other nutraceuticals. The SYNERGIC double-blinded RCT (SYNchronizing Exercises, Remedies in Gait and Cognition) evaluated the synergistic potential of vitamin D supplementation combined with cognitive and physical training on cognitive function and mobility in older adults with MCI (NCT02808676, Table 1). While this trial was terminated early due to the COVID-19 pandemic, and did not meet the participant recruitment target, the trial protocol and results have been published [35,36]. A total of 175 participants diagnosed with MCI were randomized into 5 study arms (with each arm comprised of 34 to 37 participants): 1) physical exercise (aerobic exercise and resistance training) + cognitive training + vitamin D (10.000IU/week), 2) physical exercise + cognitive training + placebo, 3) physical exercise + sham training + vitamin D, 4) physical exercise + sham training + placebo, or 5) balance and toning + sham training + placebo. The interventions were 3 times per week over a 20-week period. The primary outcomes included the ADAS-Cog13 and the Plus variant, measured at baseline, at 6 months and after 12 months (post-intervention follow-up). In a subset of participants functional brain connectivity was also assessed, but no significant correlations with lifestyle intervention effects were found. [37]Although the study was underpowered due to its early termination and some of the comparisons did not withstand false discovery rate (FDR) correction, physical exercise with cognitive training significantly improved ADAS-Cog-13 scores, driven by improvements in episodic memory, attention, and orientation [38]. These changes remained significant at the 12-month follow-up as well [38]. ADAS-Cog-Plus did not improved significantly by any combination of the interventions [38]. While physical exercise alone or combined with vitamin D supplementation did not improve cognition,[38] it still emerged as the primary contributor to improvements in functional brain connectivity (Table 2) [37].

3.4.4. *Lifestyle interventions combined with Souvenaid*

Souvenaid® is a multi-nutrient formulation comprising DHA, EPA, uridine monophosphate, choline, B-vitamins (B12, B6, folic acid), vitamin C, vitamin E, phospholipids, and selenium. Preclinical studies have demonstrated the neuroprotective properties of this combination of nutrients, suggesting a potential damage reduction in neurological conditions associated with AD [39,40]. A pilot clinical trial involving 225 patients with mild AD dementia evaluated the effects of Souvenaid® (Fortasyn Connect) over a 12-week period. The results of cognitive tests showed improved delayed recall, with a sub-analysis indicating that the benefits were most pronounced when supplementation began early in the prodromal stage of AD [41]. A 2-year clinical trial, with optional 1-year double-blind extension, tested Souvenaid® in 311 prodromal AD patients (LipiDiDiet, Netherlands clinical trial registration number NL1620)and reported a significant slowing of cognitive-functional decline (CDR-sum of boxes, CDR-SB), and attenuated hippocampal atrophy at 2 years. No significant effect was reported on the primary outcome (5-item NTB), but the cognitive decline in the study population was less than expected, reducing statistical power [42]. Data from the 3-year time point confirmed the cognitive benefits of Souvenaid®, in terms of primary and secondary endpoints (i.e., 5-item NTB score, NTB memory domain, CDR-SB) and reduction of brain atrophy [16]. Clinically, these results were estimated to translate into a delay of 7 to 10 months in disease progression, based on analyses using various time-component tests from the 2-year data [43].

The 6-month multinational, proof-of-concept Multimodal Preventive Trial for Alzheimer's Disease (MIND-AD$_{mini}$), conducted within the World-Wide FINGERS (WW-FINGERS) network, investigated the feasibility of FINGER-based lifestyle intervention (nutritional guidance, physical activity, cognitive training, social activities, and monitoring of vascular and metabolic risk factors) with or without Souvenaid®, compared with standard of care (NCT03249688) in 93 patients with prodromal AD. The primary focus of this trial was on feasibility outcomes, while adherence to healthy lifestyle changes was examined as a secondary outcome [17,44]. Change in the CDR-SB was also evaluated as exploratory outcome. The study showed good feasibility and excellent adherence to the combined intervention (Table 2), which seemed to additionally have a benefit on CDR-SB. These positive results pave the way to larger trials validating the clinical efficacy of the combination of Souvenaid® + FINGER multidomain lifestyle intervention in people with prodromal AD.

The larger 2-year Dutch FINGER-NL trial (NCT05256199, Table 1) is currently investigating the effects of combined Souvenaid® and multidomain lifestyle intervention in 1210 individuals at risk of dementia, due to the presence of 2 or more modifiable risk factors plus either SCD or family history of dementia [45]. FINGER-NL is also part of the WW-FINGERS network [13]. Integrating lessons learned during the COVID-19 pandemic, it adapted a hybrid design involving a digital intervention platform with custom-made training materials (intervention group) or general lifestyle health advice (control group). The trial was estimated to be completed in 2025, with results on its primary outcome—change in NTB-based composite scores—anticipated to be

available early 2026.

3.4.5. Lifestyle intervention combined with Epigallocatechin gallate

Epigallocatechin gallate (EGCG) is a flavanol from green tea, with a good safety profile and broad mechanism of action including antioxidant activity, protection against neuroinflammation, disaggregation of tau, along with potential regulation of insulin signaling [46,47]. More than 100 clinical trials for a broad range of therapeutic areas have been conducted, including for various malignant tumors, obesity, and neurological conditions such as multiple sclerosis, AD, Down syndrome and Parkinson's disease. Outcomes have been mixed, possibly also related to EGCG's erratic bioavailability [48]. Because EGCG can easily undergo modifications or inactivation by concomitant milk consumption, ingestion after a fasting period, with at least 30 min prior to breakfast, has been recommended [48]. A 12-month clinical trial, enrolling 84 patients with Down syndrome, has shown improvements in visual recognition memory, inhibitory control, and adaptive behavior following EGCG (9 mg/kg/daily dose) combined with cognitive training [49]. The efficacy of EGCG in combination with multimodal intervention (dietary guidance, physical exercise, psychoeducation, social activities and cognitive training) in slowing down cognitive decline was assessed in the PENSA study in *APOE-ε4* carriers with SCD (NCT03978052, Table 1) [50]. This randomized control trial enrolled 129 *APOE-ε4* carriers, who were allocated to 1 of 4 treatment arms: EGCG (300-500mg/day) combined with a multimodal intervention; placebo combined with a multimodal intervention; EGCG with lifestyle recommendations; and placebo with lifestyle recommendations [51,13, 52]. . The PENSA study is part of the WW-FINGERS network,[13] with a multimodal intervention adapted from the FINGER trial [10]. Following a 12 months intervention, no statistically significant change has been observed in the study primary outcome - change in global cognition assessed by modified ADCS-PACC, with inclusion of tests of executive functions (PACC-exe) (Table 1). Nonetheless, exploratory analysis indicated that participants receiving the combined lifestyle intervention and EGCG were 2.6 times more likely to show cognitive improvements, compared to those receiving lifestyle intervention plus placebo. This group also demonstrated greater improvements in insulin resistance and mediterranean diet adherence[51] compared to those receiving lifestyle and placebo intervention, and both lifestyle intervention groups improved in physical fitness. Notably, significant cognitive benefits in the multidomain intervention + EGCG group were found after a three-month washout period, when compared to participants receiving multidomain intervention + placebo. Furthermore, all structured lifestyle intervention groups - whether paired with EGCG or placebo- outperformed those given recommendations alone in terms of improvements in some of the cognitive measures [51]. Overall the study indicated the feasibility and potential therapeutic benefits of combination interventions for a population at risk of dementia [52].

3.5. Multimodal lifestyle interventions combined with pharmaceutical compounds

3.5.1. Lifestyle intervention combined with Metformin

Increasing evidence highlights that pharmacological strategies for decreasing insulin resistance and preventing T2D may also help reduce the risk of cognitive impairment [53,54]. Metformin, the first-line treatment for T2D, has been identified as a promising repurposed pharmaceutical agent to prevent or delay cognitive impairment. In an open-label trial, metformin (750mg/day) was administered in combination with multidomain intervention (physical activity and dietary modification) to individuals with MCI and T2D or prediabetes. The trial aimed to enroll 360 patients, with a 2-year follow-up (clinicaltrials.gov registration nr: NCT02409238, Table 1), but it did not meet its recruitment goals and was terminated due to a combination of lack of funding, retirement of the main investigator, and the COVID-19 pandemic.

The ongoing METformin and FINGER Intervention to Prevent Cognitive Impairment and Disability in Older Adults at Risk for Dementia (MET-FINGER) trial, also part of the World-Wide FINGERS network, is an innovative 2-year multinational phase-IIb RCT (clinicaltrials.gov registration nr: NCT05109169, Table 1) combining metformin with multimodal lifestyle intervention [22]. This combination trial bridges the gap between pharmacological and non-pharmacological strategies for dementia prevention and uses a novel precision prevention approach, as it targets an *APOE-ε4* enriched population of 600 older adults (60–79 years) at increased risk of dementia, identified via assessment of vascular risk factors and cognitive screening [11,22]. The structured multimodal lifestyle intervention (SMLI, an optimized FINGER model) is combined with metformin when appropriate (active arm), and compared with self-guided lifestyle intervention (control arm). Participants allocated to the SMLI and at increased risk of T2D are further randomized to additionally receive metformin 2000mg/day, metformin 1000mg/day, or placebo (double-blind), with a trial-within-trial study design. This pragmatic approach mirrors potential real-life scenarios where disease-modifying treatments are given to specific at-risk populations for whom they are most effective. The primary outcome is change in global cognition (NTB overall score). Recruitment is expected to be completed by the end of 2025. This trial is expected to provide critical insights for developing and refining innovative dementia prevention strategies, focusing on delivering the most effective solutions to the right individuals at the optimal time.

3.5.2. Lifestyle intervention combined with Homotaurine (Tramiprosate)

Tramiprosate and its derivative valiltramiprosate (ALZ-801) are small molecules reported to inhibit Aβ42 aggregation into toxic oligomers, by stabilizing Aβ42 through binding at specific sites including Lys16, Lys28 and Asp23 [55]. A phase III clinical trial of Tramiprosate in AD patients failed to meet the primary efficacy endpoints, but a subgroup analysis revealed significant cognitive improvements, measured by ADAS-Cog scores, and a positive trend on CDR-SB, in *APOE-ε4* homozygous participants with milder cognitive decline [56]. Tramiprosate efficacy combined with multidomain intervention was tested in the EMuNI RCT recruiting patients with SCD (NCT03382353, Table 1) [56]. Participants were randomized to 1 of 3 study arms: the active control intervention arm (n=41) received educational training, the partial intervention arm (n=45) received 100mg/day of Tramiprosate along with nutritional guidance, and the multilevel intervention arm (n=48) received 100mg/day of tramiprosate over the course of a year combined with nutritional guidance, physical exercise, and cognitive training [57]. Outcome measures included the RAVLT delayed recall test and composite scores of global cognition, memory, attention, executive and visuospatial scores, as well as structural and functional imaging [57]. The intervention adherence reported was 80 % or higher for all arms, and one of the primary cognitive outcome measure (attention-executive composite score) indicated a beneficial effect for the multilevel intervention, compared to the control group (Table 2) [58].

3.6. Other approaches

Our search strategy additionally identified the ongoing Precision Medicine Approach for Early Dementia & Mild Cognitive Impairment (EVANTHEA) trial (NCT05894954, Table 1), described as a pragmatic, randomized, controlled trial to evaluate the effectiveness of a precision medicine treatment approach for early dementia and MCI. The trial protocol seems to have been based on a published case report series of 10 patients [59]. EVANTHEA aims to recruit 72 participants aged 45 to 76 years, randomized to a 9-month precision medicine treatment approach or a 9-month standard-of-care treatment. The description of the combination intervention lists a very broad range of supplements, hormones, medications, and other lifestyle and nonpharmacological components that are meant to be tailored to a broad range of laboratory tests and

other participant characteristics. It is, however, unclear how this will be implemented.

Results from a recent RCT investigating the effect of multidomain lifestyle intervention with multi-nutrient supplements—multivitamins, Omega-3 fatty acids (1680 mg), curcumin (800 mg), vitamin C (1g), vitamin B12 (500 mg), CoQ10 (200 mg), lion's mane (2g), Super Bifido Plus Probiotic (1 tablet/day), and magnesium (144mg)— in MCI and early AD patients (NCT04606420, Table 1) has been recently reported [60]. The trial had not met its original recruitment aim of 100 participants and randomized 51 individuals to either the lifestyle intervention (physical exercise, dietary guidance, stress management) plus supplements or control (usual care) arms, with the aim of offering all individuals in the control arm a crossover to intervention after 20 weeks (i.e., individuals in the lifestyle arm continue the intervention for 40 weeks in total). Results were published after the first phase of the 20-week randomized controlled part of the study, with significant changes reported (albeit with 1-tailed statistical tests) on most primary cognitive outcomes on CGIC, CDR-SB and CDR Global tests, along with borderline significance in the ADAS-Cog test (Table 2). Further significant changes in plasma amyloid β42/40 ratio, along with LDL cholesterol levels were also reported [60].

4. Discussion

4.1. Key methodological points

Recently, numerous modifiable risk factors of dementia have been identified, affecting dementia risk to different extents throughout the lifespan [8]. The long preclinical stage of AD, which precedes cognitive impairment and the onset of dementia, offers a valuable window of opportunity for prevention [7]. Due to the complex and multifactorial nature of ADRD, precision medicine and combination therapy approaches, integrating lifestyle interventions and pharmacological treatments to target multiple disease pathways may be more effective. Combining pharmacological and non-pharmacological interventions has yielded positive results in chronic disorders linked to ADRD (i.e., T2D, cardiovascular disease), and has the potential to promote sustained clinical benefits, reduce possible adverse events of drugs, and improve overall intervention adherence in older adults at increased risk for dementia.

Our systematic review identified a total of 12 RCTs testing combination therapies of pharmacological compounds or nutraceuticals and multidomain lifestyle interventions. These combination RCTs exhibit significant variability in key aspects of their design, such as the type and dosage of agents administered, target populations and stage across the AD continuum, intervention duration, and the composition and intensity of the intervention domains.

About half of the reviewed combination RCTs had published results. While some of the RCTs reported cognitive benefits, there was variability in the findings. For example, in the MAPT trial, while the primary outcome analysis did not show significant between-group differences, improvements were reported in at-risk subgroups when comparing lifestyle intervention plus nutraceutical versus placebo arms [15,31]. In the SYNERGIC RCT, lifestyle intervention improved ADAS-Cog-13, when compared to the control group, albeit without a combined effect observed following vitamin D administration [37,38]. In PENSA trial, combining lifestyle intervention with EGCG showed a trend toward cognitive improvement that became significant after a three month washout, indicating potential long term benefits in *APOE*-ε4 carriers with SCD [51]. In the EMUNI trial, a significant intervention effect on the attention- executive composite score was reported in the multidomain intervention group when compared to control group following 12 months of tramiprosate treatment [58]. Furthermore, a small trial in MCI and early AD reported some benefits in cognitive/functional outcomes following a combination of multi-nutrient supplementation and lifestyle intervention when compared to the usual care control group [60].

4.1.1. Evidence-based selection of pharmacological agents for combination therapies

A range of pharmacological formulations were integrated with lifestyle interventions in combination therapies. Supplements and medical food such as omega-3 compounds, vitamin D, and Souvenaid, which are generally available over the counter, have been suggested to have beneficial effects on cognition. However, no robust intervention benefit was found for omega-3 or vitamin D supplementation in combination with multidomain lifestyle interventions. This is in line with the 2019 WHO guidelines for cognitive decline and dementia risk reduction, which noted the lack of sufficient evidence for polyunsaturated fatty acids as a preventive nutraceutical [61]. On the other hand, Souvenaid has shown significant cognitive-functional benefits in prodromal AD [43].

With aging being the leading risk factor for ADRD, major efforts are underway to therapeutically target the processes that go awry with aging that have also been implicated in the pathophysiology of ADRD, including inflammation, impaired autophagy, mitochondrial dysfunction, vascular dysfunction, epigenetic changes, and synaptic loss. And given the same biological aging mechanisms underlie common chronic diseases of aging (eg, cardiovascular diseases, metabolic diseases), it is worth testing repurposed drugs already approved for these indications for dementia prevention. Drug repurposing approaches provide the added advantage of established safety profiles. Similar approaches have enabled the development of successful therapies for, e.g., cancer, HIV, or Parkinson`s disease [62,63]. The ongoing MET-FINGER trial is among the first examples of a multidomain lifestyle plus repurposed drug combination therapy. Given the link of T2D with cerebrovascular disease and AD, and the potential beneficial pleiotropic effects, including anti-inflammatory, neuro-protective, and anti-senescence effects, metformin is a very suitable candidate for drug-repurposing in dementia prevention. Other T2D medications, e.g., glucagon-like peptide-1 (GLP-1) agonists, may also be relevant for future combination therapies [64].

Novel disease-modifying therapies (DMTs) also represent promising candidates for integration into combination therapies. Anti-amyloid β antibody therapies (lecanemab and donanemab) are currently approved by several regulatory authorities in the EU and elsewhere for treatment of MCI and mild dementia due to AD and notably, the Food and drug administration agency (FDA) has recently approved the subcutaneous formulation of lecanemab for weekly maintenance dosing following initial intravenous therapy [65]. However, eligibility for these DMTs is limited, and *APOE-ε4* homozygous patients have a higher risk for serious side effects [2,66,67]. While their current availability and mode of administration (infusion) is not optimal for integration with lifestyle interventions, this may change if equivalent efficacy can be achieved through less frequent dosing or subcutaneous administration. Of note, efficacy and safety in preclinical AD and more advanced stages of AD dementia have not been established [66]. An evidence-based, expert consensus process could speed up the search for candidate DMTs for combination therapy RCTs. Global drug selection initiatives have been already developed for, e.g., Parkinson's disease. Selection criteria for novel or repurposed pharmacological agents for combination therapy RCTs will likely require a multilayered approach, considering, e.g., their probable added benefit, safety profile, and feasibility for combination with multimodal lifestyle interventions.

4.1.2. Identification of target populations

Effective interventions require identification of the at-risk target groups that are more likely to benefit. Personalized approaches could be implemented based on individual risk profiles, including, e.g., age, genetic predisposition (such as *APOE-ε4* allele), family history of memory impairment, comorbidities, and other specific modifiable risk factors, with interventions tailored and delivered in a manner that can be sustained by the individual. Four of the combination RCTs we identified considered the presence of SCD as enrichment strategy (Table 1). All

FINGER-based combination RCTs (MIND-AD$_{mini}$, MET-FINGER, PENSA, FINGER-NL) included older adults (≥60 years) with modifiable risk factors, identified in some RCTs based on validated multifactorial dementia risk scores such as CAIDE [68]. Additionally, dementia risk factors such as T2D, or genetic risk such as the *APOE-ε4* allele were also reflected in the design of MET-FINGER, IRMCI and PENSA RCTs. In MET-FINGER, participants are randomized in 2 steps, so only those who can benefit from metformin -because of central obesity or impaired glucose metabolism but no T2D – are randomized to receive the experimental drug (metformin or placebo) [22]. Ultimately, the goal is to optimize the target group selection, with higher potential for therapeutic response, ensuring also adequate statistical power to assess the experimental intervention in a given RCT. Overall, recruitment strategies need to be further developed for efficient enrollment of study participants from various sources including hospital settings (such as memory clinics, brain health clinics), the general population, and readiness cohorts with available data for pre-screening. Ensuring diversity across ethnic, sociodemographic, and economic backgrounds remains a key priority, which has been so far inadequately addressed in combination trials. Multinational and multisite trials, such as MET-FINGER, provide the possibility for recruitment of more diverse populations [22]. In existing platforms and networks, such as World-Wide FINGERS, where lifestyle-based multidomain intervention trials are tested in populations from diverse racial and ethnic groups (e.g., Caucasians, Afro-Americans, Mestizo, Malay, Indian, Chinese) [69–71], understanding the variations in key factors affecting cognitive trajectories (e.g., education, socio-economic status, genetic make-up), can also facilitate development of multinational combination trials with better representation of populations often not included in ADRD RCTs.

4.1.3. Biomarkers and biorepositories

Recent biomarker developments could greatly facilitate implementation of easily accessible (e.g., blood-based) markers for disease processes in RCTs to select suitable target populations and/or investigate responses to combination therapies;[72] a notable example is the recent FDA approval of the Lumipulse G blood test, which measures pTau217/ß-Amyloid 1-42 plasma ratio and offers a less invasive alternative to PET scans for AD diagnostics [73]. Large ongoing international projects are currently testing the real-world implementation of early detection tools for AD (eg, AD-RIDDLE) [74]. The identification and validation of novel biomarkers and multi-marker risk and disease biosignatures, along with creating the framework for large biorepositories, are essential for advancing combination RCTs. As RCTs become increasingly complex, the interpretation of biomarker findings may also be challenging, particularly in combination and add-on trial designs. Robust biomarker frameworks will be critical to guide timing and personalization efforts of multidomain interventions [7].

In addition to biomarkers of AD pathology (Aβ42/40 ratio, ptau217, etc.), emerging biomarkers that reflect the biological processes of aging are highly relevant for prevention trials given aging is the primary risk factor for sporadic AD. Current progress in biomarker development encompasses the full spectrum of aging biology, including inflammation, cellular senescence, synaptic dysfunction, vascular dysfunction, aberrant proteostasis, mitochondrial oxidative stress, metabolic dysfunction, and epigenetics [75]. As these biomarkers become validated, future studies can leverage these for enriching trial populations that would most likely benefit based on the mechanism of action of the intervention.

4.1.4. Study design for combination RCTs

The design of lifestyle intervention combination RCTs for ADRD, albeit recent, has advanced considerably in the last decade. As risk factors for ADRDs were better characterized, study designs evolved from early trials incorporating 2 or 3 intervention components (eg, MAPT or EMuNI), to more complex multidomain approaches (eg, FINGER-based). With this shift, key design elements such as intervention intensity and duration, level of personalization, sample size calculations, and participant allocation have also become increasingly complex. Earlier studies typically featured shorter interventions with smaller sample sizes and were often underpowered, which likely contributed to the lack of observed intervention benefits in some RCTs. More recently, intervention durations have spanned between 12 and 36 months, with larger sample sizes. Nonetheless, heterogeneity in intervention intensity, due to different doses or variations in intensity and mode of delivery per lifestyle domain, may influence both intervention effectiveness and participant adherence.

Potential interactions between intervention components may further contribute to the heterogeneity of RCT findings. These challenges underscore the need for more standardized combination RCT methodologies. Despite substantial progress, further innovative study designs are needed to better capture long-term intervention effects, accommodate individual variability in risk profiles, and improve scalability for real-world applicability (Fig 2). Crucially, the impact of an individual's risk or disease profile on shorter- and longer-term effects of interventions remains unclear.

The integration of the right pharmacological treatments with the most suitable lifestyle interventions at the appropriate risk or disease stages needs to be systematically explored across the AD continuum, to leverage potential synergistic and additive therapeutic effects, and minimize risk of adverse events. Statistical considerations are critical in optimizing study design. In combination RCTs, factorial (or modified factorial) study designs are usually needed to demonstrate the contribution of each intervention (lifestyle or pharmacological) to the combined effect and to understand whether the combination therapy is additive, antagonistic, or synergistic [7]. However, the 4-arm classic 2×2 factorial design requires a larger sample size. Innovative design elements, such as adding new study arms to existing trials or incorporating precision medicine strategies where treatments are tailored to individual participant profiles could increase the effectiveness of an RCT. Additionally, reducing the size of the control group through adaptive designs could improve study efficiency and ethical feasibility. Emulated trial alternatives such as using historical or real-world data to model control groups could reduce the need for large standard care groups; however, caveats include potential differences in patient characteristics, data collection methods, standard of care, and other confounding factors. Moreover, combination RCTs could accelerate translation into clinical practice by evaluating multiple therapies simultaneously, optimizing treatment strategies, and identifying synergistic effects more efficiently [7]. By incorporating lifestyle interventions, these combination trials could provide a multidimensional approach to treatment, improving long-term health outcomes. This is particularly important in individuals at risk of dementia, where combining pharmacological and lifestyle strategies may yield greater clinical benefits than either approach alone.

Driven by the need for global collaboration and methodological harmonization of multimodal dementia prevention trials, the FINGER intervention model is now being tested, adapted, and optimized across diverse geographical and cultural contexts. The World-Wide FINGERS network,[13] currently counts 70 participating countries, with a portfolio of at least 22 RCTs completed, ~25 ongoing or in planning stage. Promoting prospective harmonization of study designs, including consideration of intervention aspects such as intensity, frequency, participant adherence, and duration, along with standardized outcomes and possibilities for data sharing will enable joint analyses and cross-study comparisons. Integrating the identification of biomarker profiles to support risk stratification, disease status determination, monitoring of disease progression and treatment effects will generate robust evidence to guide combination therapies for dementia risk reduction.

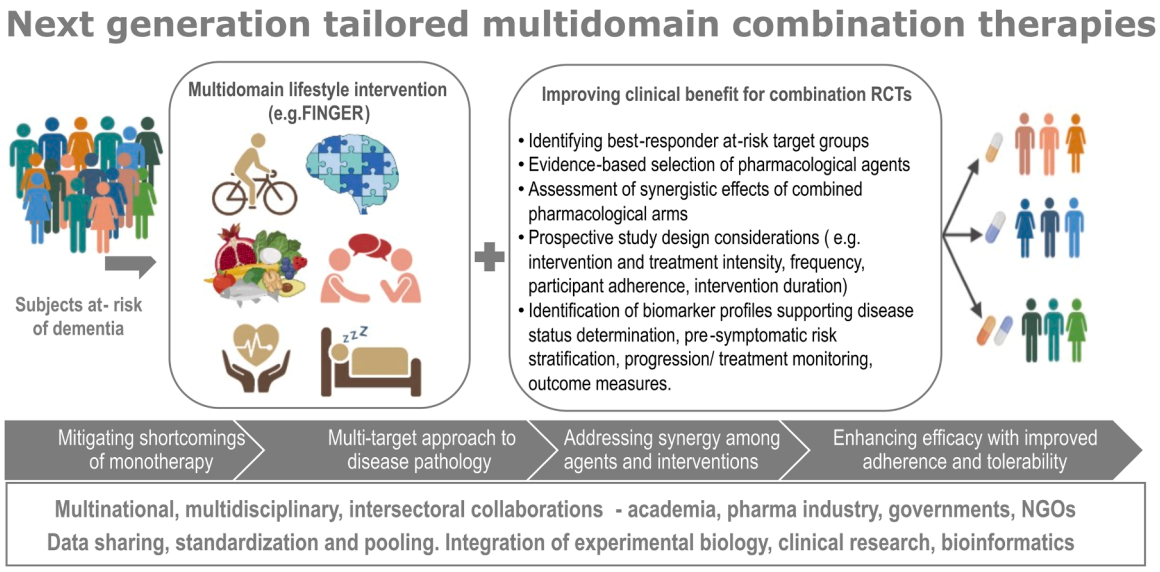

Fig. 2. Schematic representation of the study design recommendations for improved clinical benefit for the next generation tailored multidomain combination therapies(Created with BioRender.com). Abbreviations: FINGER, Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability; NGO- Non governmental organization; RCT, randomized controlled trial.

4.2. Limitations of this review

Based on GRADE guidelines,[76] some limitations were identified. Firstly, studies registered on the major clinical trial databases were searched, leading to a potential bias in the study location, as only trials and articles written in English were included. Secondly, potential publication bias must be acknowledged, as clinical trials with significant results are more likely to be published. Moreover, trials were included regardless of whether they had resulted in any publications. Furthermore, results from these RCT studies may not be generalizable beyond the scope of the specific combination of intervention, administered doses, study population, and duration of the intervention. Thus, the evidence-based classifications are presented in the context of these limitations.

4.3. Concluding remarks and future directions

These studies have provided preliminary evidence supporting the efficacy of combination therapy approaches that simultaneously target multiple risk factors and disease processes. Given the progressive nature of ADRD, certain therapeutic targets may be more effectively addressed in different stages of the disease continuum. Timing and sustainability of combination therapies, along with understanding the determinants of intervention response, are thus key factors to be evaluated. Adaptive trial designs, including platform trials or response-adaptive randomization could offer flexibility to allocate participants to promising treatment arms in a dynamic manner based on real-time data from the ongoing trial. Recent biomarker developments will facilitate the implementation of easily accessible (e.g., blood-based) markers for disease processes in RCTs to, e.g., select suitable target populations and/or investigate responses to combination therapies. Innovative adaptive or platform clinical trials integrating pharmacological treatments with multimodal lifestyle interventions, and a one-size-does-not-fit-all precision medicine approach, could substantially contribute to development of effective dementia risk reduction strategies.

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Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used OpenAI's ChatGPT in order to improve the readability of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

CRediT authorship contribution statement

Erika Bereczki: Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Francesca Mangialasche:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Mariagnese Barbera:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Paola Padilla:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Yuko Hara:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Howard Fillit:** Writing – review &

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Special Article

Identifying synergistic combinations of repurposed treatments for Alzheimer's Disease

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ABSTRACT

There is considerable opportunity to fast-track novel treatments for Alzheimer's Disease (AD) through repurposing of existing licensed medications as a way of complementing ongoing drug discovery efforts. Given the complex interplay between AD neuropathological mechanisms, there is also a strong rationale that treatment benefits may be enhanced by examining combinations of treatments to identify potential synergies that would address multiple disease-modifying mechanisms. A Delphi consensus programme combined with a pragmatic analysis of primary care data has identified a series of individual and combined therapies that warrant further investigation in pre-clinical and clinical trials. These include treatments which target well-established neurodegeneration pathways and more explorative agents, including hormonal and anti-infective agents, which align to emerging hypotheses relating to endocrine and immune pathways in AD. Whilst caution is critical when considering combined therapy due to the risks of interaction and polypharmacy, this study provides valuable indications of potential synergistic drug pairs that warrant further investigation.

1. Introduction

Alzheimer's disease (AD) is a devastating neurodegenerative disease that carries a massive personal, financial, and societal impact, with an estimated worldwide cost annually of more than $800 billion [1]. New disease-modifying treatments such as lecanemab and donanemab are emerging from the drug discovery pipeline. For example, lecanemab and donanemab are now licensed in the US and UK [2–5]. Whilst the regulatory approval in some countries is a promising step forward, these treatments still only confer modest benefits [6,7] require complex clinical protocols, and are only likely to be available in selected settings for a small proportion of patients. There is also a promising pipeline of other pharmacological treatments for AD [8]. However, the pathway to approval is lengthy and uncertain. Therefore, in parallel, there is an urgent need for safe and effective compounds that can provide improved therapeutic benefits more broadly to the large numbers of patients with or at risk of developing AD. Our improved understanding of the disease biology has increasingly highlighted several different mechanistic pathways that offer targets for treatment, either alone or in combination, including but not restricted to, tau pathology, neuroinflammation, synaptic function, mitochondrial function, neurogenesis, and neuroprotection [7].

Repurposing existing licensed drugs for other indications as treatments for AD offers a promising and efficient strategy to accelerate the readiness of effective treatments and enrich the treatment pipeline. By identifying medications already approved for other conditions that may have neuroprotective, anti-inflammatory, or cognitive-enhancing effects, repurposing bypasses early-phase safety testing and leverages existing pharmacological data and real-world evidence to significantly reduce time and cost from bench to bedside [9.10].

The rationale for investigating combination therapies in AD stems from the growing recognition that the disease is not driven by a single factor but rather by a confluence of interconnected pathological mechanisms [11,12]. Current pharmacological interventions, which largely focus on single molecular targets, have provided only modest and temporary relief from symptoms, without significantly altering the underlying disease trajectory. AD is a multifactorial disorder characterised by the intricate interplay of several key pathological hallmarks, including the extracellular accumulation of amyloid-beta (Aβ) plaques, the intracellular aggregation of neurofibrillary tangles composed of hyperphosphorylated tau protein, chronic neuroinflammation, progressive synaptic dysfunction, cerebrovascular alterations, protein clearance,

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mitochondrial function, neurochemical and receptor alterations, neurogenesis, neuroprotection, medical risk factors, and lifestyle [13,14]. Although the primary focus of the current paper is to identify potential combination repurposed pharmacological treatments, it should also be acknowledged that approaches combining pharmacological and non-pharmacological interventions may also be valuable. The FINGER study (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) is a landmark proof of concept randomized controlled trial designed to assess whether a multi-domain lifestyle intervention could prevent cognitive decline in older adults at risk of dementia. FINGER showed that a combination of diet, exercise, cognitive training and vascular risk management significantly improved cognitive function in older adults at risk of dementia, with excellent long term engagement but a very modest effect size [15]. A further study has recently demonstrated that similar benefits can be achieved with an online multi-domain intervention [16] and similar improvements can also be achieved with online cognitive training [17]. These studies highlight the feasibility and benefit to deliver effective lifestyle interventions, with an excellent opportunity for the future to optimize individual components and improve personalization and to combine these approaches with pharmacological treatments to enhance benefits.

The scientific consensus is increasingly shifting towards the necessity of a paradigm change in AD drug development, moving from a singular target approach to strategies that can simultaneously modulate multiple pathways [18,19]. It therefore makes sense that the most effective treatment approaches will involve a combination of therapies targeting multiple complementary and synergistic processes and pathways as a means of reducing the incidence or progression of AD [20].

1.1. Identifying candidate repurposed drugs through a delphi consensus approach

The Delphi expert consensus methodology has been used to identify the best candidates for re-purposing as a program commencing in 2012 [9], with a second iteration in 2020 [10] and a recently completed iteration in 2025[21]. The program involves a panel of 40 global specialists in the clinical and research fields of AD treatment, industry representatives, and a parallel lay panel to advise on candidate acceptability. Members' identities were anonymised, and feedback was sought on an individual basis, rather than as a group. Panel members suggested drug candidates for initial consideration, including potential symptom– and disease-modifying therapies. The nominations were streamlined to candidates that had been suggested by at least three members, and candidates already being investigated in phase IIb/III trials were excluded. Long-listed candidates were taken forward to systematic review to examine the potential mechanisms, the pre-clinical, clinical, and epidemiological evidence supporting their candidacy. The search used pre-defined queries in MedLine, Cochrane, PsychINFO, and SCOPUS aimed at synthesising evidence concerning the putative mechanism of drug action in AD, the therapeutic effect in vitro and in animal models of AD, evidence of benefit in humans, and safety data. This systematic review was supplemented by additional salient information such as a drug's blood-brain barrier penetration, license status, posology, and route of administration. Completed reviews were circulated to the panel, and members ranked each candidate based on the strength of evidence, in addition to providing specific comments using a feedback form. Further rounds of feedback and consensus were undertaken as appropriate. Our Delphi methodology and the participating panel members are described in full elsewhere [9,10,21].

In 2012, the priority compounds included glucagon-like peptide 1 (GLP-1) analogues, angiotensin receptor blockers (ARBs), calcium antagonists, and tetracycline antibiotics [9]. The outcomes informed clinical trial prioritization and treatment development. Subsequent trials of the ARB losartan [22], the calcium channel blocker nilvadipine [23], and the tetracycline antibiotic minocycline [24] were unsuccessful. However, evidence from national registries, incident AD as a secondary outcome in clinical trials focussing on cardiovascular outcomes [25], and a phase II trial of liraglutide in people with mild-to-moderate AD all indicated benefit [26]. The GLP-1 analogue semaglutide is now moving forward as part of a large Novo-Nordisk phase III clinical trial programme [27,28].

The 2020 Delphi iteration identified the rho-kinase inhibitor fasudil, with impacts on amyloid, tau, and synaptic function, the cholinesterase inhibitor phenserine, with additional impacts on cell death pathways, and anti-viral treatments for herpes simplex as the highest priority candidates [10]. All these compounds are now being investigated in clinical trial programmes.

The most recent Delphi iteration has identified three further high priority candidates [21], the benzothiazole medication riluzole, the vasodilator sildenafil and the herpes zoster vaccine. The evidence supporting these three treatment approaches and the most promising therapies from the two earlier Delphi consensus exercises is summarised in Table 1.

1.2. Identifying candidate combinations

It is highly likely that targeting different AD pathways may elicit combined independent benefits of the different treatment approaches, but in an ideal scenario, there would be additional synergistic benefits. The various pathological changes and pathways involved in AD are not independent but are intricately interconnected, forming a complex web of interactions that drives the progression of the disease pathology and related symptoms [82]. For instance, the accumulation of Aβ plaques and the formation of tau tangles can synergistically promote neuronal damage and cognitive decline [83]. Neuroinflammation can be triggered by the presence of Aβ plaques and tau, which in turn exacerbates their accumulation and contributes to neuronal loss [84]. Synaptic dysfunction can arise as a consequence of both Aβ and tau pathology, as well as the inflammatory milieu [85]. Furthermore, cerebrovascular dysfunction can impair the clearance of Aβ plaques, promote neuroinflammation, and induce oxidative stress, all of which contribute to neurodegenerative processes [86].

Beyond the core neuropathological hallmarks, cerebrovascular dysfunction also plays a significant role in the pathogenesis of AD [87]. Vascular risk factors such as hypertension, hyperlipidemia, and diabetes are associated with an increased risk of developing AD and can exacerbate its progression [88]. Cerebrovascular dysfunction can lead to reduced cerebral blood flow, hypoxia, and impaired clearance of Aβ plaques from the brain. This complex interplay underscores the necessity of developing combination therapies that use a smart approach to targeting AD pathways to achieve the maximum synergistic benefit on disease progression [20].

In order to identify potential combinations of high priority candidates as repurposed treatments for AD, we utilized two different approaches. Firstly, we focussed on the candidate therapies for repurposing identified by our Delphi panel from each of our three completed programmes. Eligible combinations focussed on one of the compounds identified as the highest priority candidates from any of the programmes, excluding compounds that have failed to confer benefit in subsequent RCTs, in combination with another high priority or shortlisted candidate. This limited the selection to treatments that were already identified as good candidate therapies. Combinations within this pool of compounds with the potential for synergies were then identified by the authors of the current paper through literature review, and the best combinations were prioritized by consensus by the author group. The nine highest priority combinations and the potential mechanistic synergies for these combinations are described in Table 2.

Secondly, we have taken a more data driven approach, examining the Clinical Practice Research Datalink (CPRD) primary care database in the UK to identify any treatment combinations associated with a reduced incidence of AD. We have previously reported an inverse association between individual drug prescriptions and AD incidence, based on a

Table 1
Summary and supporting evidence for tretment candidates arising from three Delphi consensus programmes.

Drug	Mechanism of action	Pre-clinical data	Clinical data
GLP-1 RA	· Neuroprotection through GSK3β and tau phosphorylation pathways [29,30], · Protection against oxidative stress and apoptotic pathways [31]	· In vitro GLP-1 RA reduces intracellular amyloid precursor protein (APP), Aβ and Fe2+-induced neurodegeneration [29] · In vivo research suggests rescued synaptic plasticity and cognitive function, and decreased AD pathology [31]	• National registry cohort studies show a reduced incidence of AD in people taking GLP analogues [25] • Secondary analysis of RCTs of GLP analogues focussing on cardio-vascular outcomes indicate reduced incidence of AD [25,32], • A pilot study of 38 patients with AD demonstrated significant benefits in glucose metabolism for liraglutide compared with placebo [33]. A phase 2b trial of liraglutide in mild-moderate AD indicated significant benefits in cognition and medial temporal atrophy [26]
Fasudil	· Reduction in Aβ plaque levels via the Dkk1-driven Wnt–PCP pathway [34] · Reduction of inflammation levels [35], rescue of synaptic damage [36], and reduced dendritic arborization [37]	· There is consistent evidence that fasudil protects synaptic function, reduces amyloid burden and rescues cognition in a range of animal models of AD [34,36,38],	· The safety and acceptability of this drug was shown in studies focussing on ischaemic heart disease [39] · One small study of people with MCI and AD suggested cognitive benefits with fasudil compared to nimodipine [40]
Phenserine	· Reduces apoptosis and impacts on cell death pathways [41] · Additional actions include suppression of IL-1β production [42], reduction in glutamate-induced excitotoxicity [43], protection against oxidative stress [43], and reduction in Aβ plaque levels [44] · Increase in production of brain-derived neurotrophic factor (BNDF) [43] · Inhibition of APP [44]	· Multiple pre-clinical studies demonstrated that phenserine alters cell death pathways, improves neuronal survival, and decreases APP levels in cell cultures and rodent models of AD, stroke, and head injury [44–46]	· A small RCT randomized 20 participants with mild AD to receive either phenserine (15 mg twice per day) or placebo for 3 months. The group of participants receiving phenserine had significantly better cognitive function at the 3-month time-point [47] · A phase II, 12-week RCT in 164 participants with AD indicated that (−)-phenserine (10–15 mg twice per day) had significantly better cognitive function than the group receiving placebo [48]
Herpes zoster vaccine	· Herpes zoster is thought to increase the risk of dementia by triggering neuroinflammation, generating oligomers, promoting the accumulation of amyloid plaques and neurofibrillary tangles of hyperphosphorylated tau, as well as causing vascular damage in the central nervous system and, in severe cases, encephalopathy [49]	The varicella zoster virus has recently been linked to amyloid deposition and aggregation of tau proteins [13], as well as cerebrovascular disease that resembles the patterns commonly seen in AD, such as small to large vessel disease, ischemia, infarction, and haemorrhage [14,18,19]. In addition, reactivations of the varicella zoster virus may in turn reactivate the herpes simplex virus in the brain [21]	Recent well-conducted epidemiological studies have consistently indicated a correlation between vaccination against herpes zoster, mostly using the active vaccine, have indicated a significant reduction in the incidence of dementia, including AD • Systematic review of 5 studies, with almost a million participants total, suggested a relative reduction of 16 % in incident dementia [50] • In subsequent studies, there was a 20 % relative reduction and 3.5 percentage point reduction in the probability of new dementia diagnoses compared with unvaccinated individuals • [51], with consistent findings from another recent report [52] • Most evidence is with the active vaccine, but a recent study did suggest a more modest reduction in dementia risk with the recombinant vaccine [53]
Riluzole	· Inhibition of glutamatergic neurotransmission and of voltage- dependent sodium channels [54] · Protection of neuronal firing from amyloid [55,56], and potentiation of postsynaptic GABA receptor function ((78) · Increase in BDNF levels [57] · Normalisation of EAAT3 expression [58,59], and of glucose metabolism [60] · Reduction of tau [61] and Aβ plaque burden [62] · Reduction of hippocampal AChE activity and of oxidative stress [63] · Reduction in levels of disease-associated microglia [62] · Increase in dendrite density [58]	Pre-clinical evidence in mice is in broad agreement that riluzole improves cognition in various mouse models of AD [64,59–62,65],.	One small 6-month clinical trial in 50 people with probable AD (MMSE, 19–27) reported that riluzole had a protective effect on brain glucose metabolism compared with placebo, with the most robust effect in posterior cingulate, and effects in precuneus, lateral temporal, right hippocampus, and frontal cortex [66]. Although underpowered for statistical evaluation, there were also numerical benefits on cognitive outcomes and a significant correlation between cognitive outcomes and PET biomarkers.
Sildenafil	· Increase in neurite growth [67] · Reduction in tau hyperphosphorylation [67–69] · Improvement in central nervous system hemodynamic function and increase in oxygen levels [70] · Reduction of hippocampal Aβ42 levels and in GFAP expression [71] · Reduction in α-synuclein levels and oxidative stress [72] · Rescue of PKG/pCREB signalling [73]	· Pre-clinical evidence in mice is in broad agreement that riluzole improves cognition in various mouse models of AD [73,78–80],	· Epidemiological studies reporting contrasting findings on the protective effect of sildenafil on AD · One small open study of sildenafil in 8 patients with AD using a novel MRI technique to examine cerebral oxygen metabolism demonstrated a significant improvement in cerebral hemodynamic function with sildenafil treatment [70] · A further small MRI study in 10 patients with AD suggests that sildenafil appears to normalize

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Table 1 (*continued*)

Drug	Mechanism of action	Pre-clinical data	Clinical data
	· Decrease in GSK3β and CDK5 activity and increased BDNF and Arc levels [69] · Increase in levels of activated JNK (p-JNK) [74] and up-regulated heme oxygenase-1 [75] · Regulation of NO-cGMP signalling [76] · Down-regulation of pro-apoptotic proteins in aged mice [77]		spontaneous neural activity [81] No RCTs have been conducted

case-control analysis [109]. Building on this, we undertook a retrospective analysis of the same UK CPRD dataset of 40 million medical records to investigate potential synergistic effects between drug pairs in relation to AD susceptibility. Specifically, we evaluated whether combinations of two drugs, prescribed five to ten years prior to the index date, were associated with a modified risk of AD beyond the additive effects of each drug individually. To assess this, logistic regression models were fitted for each drug pair, including both main effects and their interaction term. The binary outcome variable indicated case/-control status, and the predictors included indicators for exposure to each drug and their interaction. The evaluation specifically required a significant synergy score for the two identified therapies, as well as overall benefit, to increase the robustness of the analysis. The synergy score for a drug pair was defined as the z-value of the interaction term coefficient from this model. The significant synergistic pairings and their hypothetical synergistic mechanisms are shown in Table 3. Several drug combinations exhibited strong evidence of protective synergy. Notably, combinations such as beclometasone and salbutamol ($z = -14.03$) [110–112], clindamycin [113] and phosphate ($z = -11.25$) [114], and estradiol [115] and folic acid ($z = -9.96$) [116] showed greater protective effects than expected based on their individual associations. Many of the synergistic pairs involved hormonal therapies or anti-infective agents, consistent with emerging hypotheses linking endocrine and immune pathways to AD susceptibility. These findings highlight drug–drug interactions as a potentially important and underexplored factor in modulating AD risk. However, the exact biological mechanisms remain speculative, with further experimental validation needed as these associations only indicate correlation and not causation. It should also be acknowledged that there are many potential confounding factors with real-world datasets, and that the majority of candidates identified through this approach have not been shown to be effective therapies in further evaluations. Nevertheless, this approach is potentially valuable in informing further pre-clinical studies to verify potential mechanisms and benefits and to identify candidate combinations. More details and possible mechanisms for synergies in these combinations are shown in Table 3.

1.3. Some caution regarding combination approaches

While combining therapies that target multiple disease pathways offers clear theoretical advantages, this approach must be considered against the backdrop of risks associated with current and future treatments, particularly in vulnerable populations affected by AD. For instance, the recent advent of anti-amyloid monoclonal antibodies has highlighted specific safety concerns such as Amyloid-Related Imaging Abnormalities (ARIA), which can manifest as cerebral edema or microhemorrhages [120]. These risks are especially pertinent in the target population of older adults, many with Mild Cognitive Impairment (MCI) who are already at an increased baseline risk for falls, confusion, and cognitive fluctuations. In the broader group of individuals with AD or other dementias, the majority of people are over 80, many presenting with multiple comorbidities such as cardiovascular and renal disease, necessitating numerous concomitant medications [121]. Introducing a combination therapy into such a complex polypharmacy regimen significantly increases the potential for adverse drug-drug interactions and cumulative tolerability issues. These patient-centric challenges are mirrored by methodological hurdles, including the increased complexity and cost of clinical trial designs and the additional regulatory scrutiny required when evaluating two or more active treatments to demonstrate the benefits of each agent as well as the combination [122]. Therefore, novel strategies such as network pharmacology and biomarker-guided precision medicine will be key to developing and optimizing patient-specific regimens that maximize benefit while minimizing harm [13,123]. Fluid biomarkers in AD offer a minimally invasive means to detect and monitor underlying pathological changes, including amyloid-beta accumulation, tau pathology, and neurodegeneration. Key CSF biomarkers include decreased Aβ42 (reflecting plaque deposition) and increased p-tau and total tau, which correlate with tangle pathology and neuronal injury. Recent advances have enabled the development of blood-based biomarkers, such as plasma Aβ42/40 ratio, p-tau181, p-tau217, and Nfl, which closely mirror CSF and PET findings and are increasingly used in clinical trials and early diagnostic frameworks [124]. These biomarkers facilitate early diagnosis, patient stratification, and treatment monitoring, and are central to the move toward precision medicine in AD. A related article in this special issue explores the integration of biomarkers in combination therapy (*Author list TBD*, 2025).

2. Conclusions and recommendations

Although it is important to be mindful of potential design, regulatory, and tolerability issues with combination therapies, the likely benefits should outweigh the risks for carefully selected, synergistic treatments. Using two different approaches—expert review and evaluation of a large real-world dataset—we have identified 17 potential combinations to inform further pre-clinical and clinical studies.

From a pragmatic perspective, low-risk treatment combinations are well suited to large-scale hybrid trial designs run substantively through digital platforms. This will have the advantage of cost-effective, well-powered trials with the power to detect the additive effect of treatment combinations as a critical proof of concept of the combination treatment approach. Although the current paper focuses on pharmacological treatment combinations, it will also be important to consider the potential additional benefits of combining treatments with lifestyle interventions to maximise benefit.

CRediT authorship contribution statement

Clive Ballard: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Janet Sultana:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Pat Doherty:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Gareth Williams:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Anne Corbett:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Anne Corbett reports a relationship with Addex Therapeutics Ltd that includes: consulting or advisory. Anne Corbett reports a relationship

Table 2
Mechanistic synergies and rationales for therapy combinations arising from review of Delphi candidates.

Priority Repurposing Candidate	Candidate Combination Candidate	Mechanistic Synergy and Rationale
Fasudil	**Fingolimod**	Fasudil primarily targets the Rho-ROCK pathway to improve cerebrovascular function and inhibit microglial M1 activation. Fingolimod modulates adaptive immunity and intrinsic CNS inflammation by preventing peripheral immune cell entry. Fingolimod also supports synaptic health via brain-derived neurotrophic factor [89–92]
	Memantine	Memantine preferentially blocks overactive extrasynaptic NMDA channels [92], protecting neurons from excitotoxicity. Fasudil improves synaptic plasticity and blood flow, creating a better environment for neurons [1]. Fasudil enhances the neuronal environment while memantine protects the neurons within it [89,92,93],
	Vortioxetine	Vortioxetine addresses neurotransmitter deficits and is a multimodal antidepressant. By antagonizing 5-HT$_3$ receptors, vortioxetine can disinhibit cholinergic and glutamatergic signalling to improve memory encoding [94]
	Rifamycin	Rifampicin disaggregates Aβ and tau oligomers in preclinical models. Fasudil inhibits RhoA/ROCK signalling to decrease tau phosphorylation. Rifampicin targets protein aggregates while fasudil improves tau clearance and cerebrovascular function [95–97]
GLP-1	**Microlithium**	GLP-1 analogues like liraglutide have shown neuroprotective effects in AD models and help maintain brain glucose metabolism. Lithium has disease-modifying properties and can be effective in mild cognitive impairment. The combination targets both metabolic dysfunction and tau pathology [98–100]
	Phenserine	GLP-1 analogues have shown neuroprotective effects by reducing amyloid and tau pathology. Phenserine is investigated as a potential disease-modifying therapy targeting APP. These agents target amyloid and tau pathology through distinct mechanisms [101–103]
Sildenafil	**SSRI (Vortioxetine / fluoxetine)**	Sildenafil increases cGMP levels, enhancing cerebral blood flow and synaptic plasticity, which can restore cognitive function in AD models. Chronic SSRI treatment can reduce Aβ deposition. These drugs enhance neuroplasticity and reduce AD pathology via distinct routes [69.104.105],
Herpes zoster Vaccine	**Anti-inflammatory**	Herpes zoster vaccination is associated with a lower risk of dementia [106], possibly by priming the immune system against viral triggers [107]. Long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) like ibuprofen has been associated with a reduced risk of AD [108]. An immune-priming effect from the vaccine could be complemented by the neuroinflammation-reducing effects of anti-inflammatory drugs

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Table 3
Potential protective synergistic effects between pairs of drugs prescribed 5 to 10 years prior to AD diagnosis. Logistic regression–derived odds ratios (ORs) and 95 % confidence intervals are reported for each drug individually and for their combined use. The strength and significance of the interaction (ie, departure from additivity on the log-odds scale) is indicated by the z-score of the interaction term from the regression model. The hypothetical synergistic action is summarised.

	Drug A	Drug B	Synergy Hypothesis
Candidate OR (95 % CI)	**Beclometasone** −0.02 (−0.04 0.00)	**Salbutamol** −0.17 (0.20–0.15)	**Anti-inflammatory:** Chronic systemic inflammation is a significant risk factor for AD. Beclometasone's potent anti-inflammatory action could reduce neuroinflammation [110]. Salbutamol, while primarily a bronchodilator, has anti-inflammatory properties [111], potentially by modulating immune cell activity or cytokine release [112]. **Beyond Respiratory:** β2 adrenergic receptors are present in the brain. Modulation by salbutamol might have direct neuroprotective effects, especially when combined with the anti-inflammatory action of beclometasone
Synergy Z Score	−0.23 (−0.26 − 0.20) −14.03		
Candidate OR (95 % CI)	**Clindamycin** −1.48 (−1.57–1.38)	**Phosphate** 0.23 (0.20 0.25)	**Microbiome Modulation:** Clindamycin is a broad-spectrum antibiotic, significantly altering gut microbiome [113]. The gut-brain axis is increasingly recognized as a key player in AD [117]. Dysbiosis can lead to increased gut permeability, systemic inflammation, and production of neurotoxic metabolites. **Cellular Energy Metabolism:** Phosphate is crucial for numerous cellular processes, including ATP production, DNA synthesis, and cell signalling [114]. While excess phosphate can be detrimental, its combination with clindamycin could suggest a complex interplay. Clindamycin's microbiome modulation could make cells more efficient at utilizing phosphate for energy or repair, or phosphate may act as a cofactor in specific metabolic pathways that are protective against AD when the microbiome is altered by clindamycin **Inflammation/Oxidative Stress:** A healthy gut microbiome influences systemic inflammation and oxidative stress [113]
Synergy Z Score	1.74 (−1.87–1.62) −11.25		
Candidate OR (95 % CI)	**Estradiol** −1.51 (−1.55 − 4.48)	**Folic Acid** −0.22 (−0.27–0.18)	**Hormonal Neuroprotection:** Estradiol has neuroprotective effects [115], including antioxidant properties, promotion of neuronal survival, modulation of neurotransmitter systems, and maintenance of cerebral blood flow [117–119] **Homocysteine Reduction and Vascular Health:** Folic acid is
Synergy Z Score	2.33 (−2.52 − 2.15) −9.96		

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Table 3 (*continued*)

Drug A	Drug B	Synergy Hypothesis
		essential for homocysteine metabolism, a risk factor for cardiovascular disease and AD. By reducing homocysteine levels, folic acid improves brain vascular health, reducing the risk of cerebrovascular pathology that contributes to AD [116] **Epigenetic:** Folate is involved in methylation, which is crucial for epigenetic regulation. Both estrogen and folate influence epigenetic modifications **Synaptic Plasticity and Neurogenesis:** Both estrogen and folate have been implicated in promoting synaptic plasticity and neurogenesis. Their combined action could lead to enhanced cognitive reserve and resilience against AD pathology

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Notes

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