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Drug repurposing for Alzheimer's disease and other neurodegenerative disorders

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Repurposed drugs provide a rich source of potential therapies for Alzheimer's disease (AD) and other neurodegenerative disorders (NDD). Repurposed drugs have information from non-clinical studies, phase 1 dosing, and safety and tolerability data collected with the original indication. Computational approaches, "omic" studies, drug databases, and electronic medical records help identify candidate therapies. Generic repurposed agents lack intellectual property protection and are rarely advanced to late-stage trials for AD/NDD. In this review we define repurposing, describe the advantages and challenges of repurposing, offer strategies for overcoming the obstacles, and describe the key contributions of repurposing to the drug development ecosystem.

The prevalence of Alzheimer's disease (AD) is growing rapidly. The global population of individuals with AD dementia is anticipated to increase from the current 57 million to 153 million by 2050[1]. There will be a disproportionate growth of AD and other dementias in low- and middle-income countries (LMICs); by 2050 71% of patients with dementia will live in these regions[2]. In addition to those with the dementia of AD, many more have mild cognitive impairment (MCI) or preclinical AD[3]. Other neurodegenerative disorders (NDDs) that are growing with the aging of the global population include Parkinson's disease and related disorders such as dementia with Lewy bodies, frontotemporal dementia and associated conditions such as progressive supranuclear palsy and corticobasal degeneration, and amyotrophic lateral sclerosis (ALS)[4]. Approval of anti-amyloid monoclonal antibodies represents an important advance in the treatment of AD but applies to an early form of the disease and rely on diagnostic and therapeutic technologies with limited availability[5]. There are many non-amyloid processes in the pathophysiology of AD that comprise important targets for new therapeutic development[6–8]. There is an urgent need to develop new therapies that will prevent or delay the onset of the pathology or symptoms of AD/ NDDs, slow the progression of the diseases, or improve cognition, behavior, function, and other neurological abnormalities.

Development of new treatments for AD/NDDs is complex, requires a development program that averages 13 years to complete, and frequently results in failure[9]. Approaches to drug development that are more likely to succeed and require more limited time and financial investment could accelerate the emergence of new therapies. Repurposed drugs approved for a non-AD/non-NDD indication are a promising source of new therapies.

We describe the potential for repurposing therapeutics for AD/NDDs and note the benefits of developing a second use of an approved medicine whose pharmacokinetics, safety toxicity, and manufacturing are known. We note the role of repurposed drugs in the current AD pipeline and describe the emergence of new technologies for the identification of candidate repurposable agents. We note the advantages of repurposing as a development strategy. We describe the challenges associated with advancing repurposed drugs, particularly the limited availability of funding and sponsors for late-stage trials if the agents are generic. We suggest possible solutions for the challenges faced by repurposing and issue a call to action for legislative changes that would incentivize programs to develop repurposable

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generic agents for the treatment of AD/NDD. We describe the central role of repurposed agents in the AD drug development ecosystem.

Discussion

Definitions

Drugs with "new uses" include agents that have been developed and marketed for one indication and are now generic and being considered for a new indication; therapies that have been developed and marketed for one indication, remain on patent, and are now being considered for a new use; and drugs that have been developed through Phase 1 for one indication, never received marketing authorization, and are now being considered for another indication[10,11]. In this article, we use "repurposing" to describe drugs that are approved for a non-AD/non-NDD indication and are being studied to determine their possible effect on the biology or symptoms of AD/NDD. Most repurposed agents are off patent generic drugs but treatments with remaining patent life can be repurposed from one indication to another. Brexpiprazole, for example, was successfully repurposed from approved indications as an adjunctive therapy for the treatment of major depressive disorder in adults and for adult and pediatric schizophrenia to approved treatment of agitation in dementia due to AD[12]. Semaglutide, a glucagon-like protein-1 (GLP-1) agonist is approved for treatment of diabetes and obesity and is being assessed in clinical trials for treatment of early AD. Both these agents are proprietary on-patent drugs being repurposed within an industry pipeline. More typical are agents such as rasagiline or rotigotine approved for Parkinson's disease and explored in repurposing programs for AD after becoming generic[13,14]. We distinguish repurposing from "repositioning" that describes agents that were being developed by a sponsor for one indication and reprioritized for a new indication as the goal for the program prior to receiving marketing authorization. "Drug reprofiling," "drug re-tasking," "drug redirecting", "drug rescue", "drug rediscovery" or "indications discovery" are alternative terminologies that have been applied to drug repositioning strategies[15,16]. Repurposing here refers to drugs that have completed non-clinical and Phase 1 clinical trial assessments.

Choosing a candidate agent for repurposing

There has been marked progress in developing advanced technologies to identify compounds with characteristics suggesting they are candidates for repurposing for the treatment of AD/NDDs. Advanced computational strategies, suggest agents that can be explored in non-clinical in vivo studies or through pharmacoepidemiologic studies and advanced to human Phase 2 or Phase 3 trials if the data consistently suggest an impact on AD (Table 1).

Genomic and multi-omics data. Genetic and genomic data based on high-throughput DNA/RNA sequencing technologies and multi-omic data from transcriptomic, proteomic, lipidomic, and metabolomic studies are available through the Alzheimer's Disease Sequencing Project (ADSP)[17], Alzheimer's Disease Neuroimaging Initiative (ADNI)[18], and AD Knowledge Portal[19], among others. Genome-wide association studies (GWAS) have identified ~100 AD susceptibility loci[20–22]. Despite progress in understanding genetic risk factors, the complex genetic architecture of AD has limited the development of new therapeutics based on these data. The data exploitation challenges have motivated the application of artificial intelligence (AI) and other computational technologies to help identify promising drug targets and candidate compounds possibly efficacious as treatments for AD/NDD[23]. Bumetanide, is an example of an approved agent, nominated as a repurposable agent based on transcriptomic studies and exhibiting properties suggesting it will be useful for treatment of AD occurring in apolipoprotein E ε4 (*APOE4* carriers)[24]. Novel non-amyloid targets are emerging as key repurposing candidates for the treatment of AD/NDD[25].

The Genetics of Alzheimer's Disease Data Storage Site (NIAGADS, https://www.niagads.org), a national genetic and genomic data repository for AD research, comprises 122 datasets and 183,099 samples (accessed March 20, 2024). The AD Knowledge Portal[19] contains upwards of 100,000 data files from over 80 studies of people with AD and related animal models. The Accelerating Medicines Partnership - Alzheimer's Disease (AMP-AD) was formed to identify biologically relevant therapeutic targets, as well as new biomarkers; the data are stored in the AMP-AD Knowledge Portal (https://agora.ampadportal.org). AlzGPS[26], a systems biology platform, enables searching, visualizing, and analyzing multi-omics data for AD drug target identification. AlzGPS contains more than 100 AD omics data sets capturing DNA-RNA-protein relationships. The Alzheimer's Cell Atlas (TACA)[27] is an AD brain cell atlas consisting of over 1.1 million single-cell/nucleus transcriptomes, covering major AD brain regions (e.g., hippocampus and prefrontal cortex) and cell types (astrocyte, microglia, neuron, oligodendrocyte, etc.). These genetic and multi-omic resources provide genomic, epigenomic, transcriptomic, proteomic, radiomic, and metabolomic data from thousands of human brains, which may translate into possible therapeutic target discovery for repurposed agents for AD. Translating these targets into repurposable therapies is facilitated by knowledge graph approaches that use computational strategies to match disease nodes and networks to known drug nodes and networks to discover drugs with repurposing potential for AD/NDD[28,29]. These approaches will identify and prioritize repurposable drugs.

Table 1 | Sources of efficacy data that may become available to support the choice of a candidate agent for repurposing

Epidemiologic studies and data repositories	Pharmacoepidemiologic studies
	Electronic medical record studies
	Genetic studies including genome wide association studies
	Omic data (genomics, proteomics, transcriptomics, metabolomics, lipidomics, connectomics)
	Drug databases
	Extrapolation from other neurodegenerative disorders
	Patient and clinical observations
Technologies	Artificial intelligence and machine/deep learning algorithms applied to big data resources
	In silico network-based drug-disease proximity assessment for repurposing
	Trial emulation of repurposed agents
	Mendelian randomization
	Cell, induced pluripotent stem cell/organoid, and animal model observations

Many types of data may suggest that an agent is appropriate for a clinical trial. There is more confidence in the success of an agent when multiple data sources converge in support of its relevance to the biological processes of the neurodegenerative disorder.

Real-world data/electronic health records. Comprehensive electronic health record (EHR) systems have substantial potential for identifying disease risk factors and new treatments[30]. Drug repurposing focuses on drugs that already exist in patient databases, and EHRs allow efficient testing of hypotheses by using massive amounts of electronically captured patient data[31]. The unique strengths of real-world data (RWD) include large patient populations useful for detecting small differences in treated compared to untreated patients, and the availability of many patient factors that can be studied without risk of recall bias. These features allow for high-dimensional covariate adjustment that minimizes confounding factors to rapidly screen potential medicines for AD/NDD[30]. Repurposing candidates with EHR support for treatment of AD include sildenafil and telmisartan[32]. The latter study used a Mendelian randomization strategy and showed that telmisartan was disproportionately effective in African Americans at risk for AD, representing a step toward the intersection of precision medicine and repurposing[33].

Clinical trial emulation. Clinical trial emulation refers to the process of mimicking a randomized controlled trial with large-scale observational RWD. The classic trial emulation platform includes these components: 1) eligibility criteria; 2) treatment strategies; 3) assignment procedures; 4) outcomes; 5) causal contrasts of interest; 6) data analytic plans; and 7) follow-up period[34]. RWD from OneFlorida+ Clinical Research Network were used in a trial emulation approach to simulate a real-world AD trial to assess the prediction of adverse events[35]. Side effect rates comparable to the original randomized controlled trial (RCT) of donepezil were generated, with a propensity score (PS) matching approach[35]. PS matching facilitates limiting bias from confounding factors by summarizing the distributions of many confounding effects in a single score based on the probability of receiving treatment[36]. Application of PS to RWD used in trial emulation improves internal validity, mitigates confounding by indication, and reduces selection bias[37]. Zang et al. conducted a trial emulation with PS adjustment to identify potentially repurposable drug candidates for AD and validated the strategy on a subset of OneFlorida+ and the MarketScan national claims database[38]. Pantoprazole, gabapentin, atorvastatin, fluticasone, and omeprazole were identified as approved agents with repurposing promise for AD. Atorvastatin has been studied in clinical trials of AD and found not to be effective; this negative interpretation is confounded given that the trial preceded current diagnostic approaches to AD[39]. Diverse targets and candidate combinations addressing targets beyond the canonical amyloid and tau processes are emerging from these interrogations.

Network proximity mapping and bioinformatics. Drug targets are embedded in complex systems of proteins that comprise the functional architecture of the cell; each drug-target interaction must be examined in this integrated context. Novel approaches, such as network-based drug-disease proximity mapping can model the relationship between drug targets and molecular disease components and serve as useful tools for efficient screening of potential new treatments for AD[32]. An unbiased and comprehensive protein-protein interaction (PPI) network based on validated physical interactions between proteins was used to identify domains or subnetworks within the PPI that are associated with specific human diseases, including AD[32]. Within this network are targets for approved drugs that may be repurposed for the treatment of AD/NDDs. Drug-target databases, such as DrugBank[40], are resources for network proximity analyses.

In addition to network proximity, bioinformatics approaches such as gene-set enrichment analysis (GSEA)[41] provide in silico approaches to repurposing drug discovery. Via GSEA of drug-gene signatures in human cell lines from the connectivity map (CMap) database, several candidate anti-inflammatory drugs (i.e., fluticasone, an approved glucocorticoid receptor agonist for asthma and other indications) were identified[42]. In an EHR search, fluticasone was significantly associated with a reduced incidence of AD. PS–stratified cohort studies further suggested that the use of mometasone (a glucocorticoid receptor agonist) was significantly associated with a decreased risk of AD compared to fluticasone after adjusting for age, sex, and disease comorbidities[42]. These network-based bioinformatics approaches are powerful in silico tools to screen candidate repurposable drugs and drug combinations for the treatment of AD/NDDs. Advancing these agents could offer alternatives to anti-amyloid therapies as well as guidance for combination therapies.

Computational strategies have been applied to explore possible combinations of repurposable treatments for AD. Using disease network and proximity matching, Fang and colleagues found that carvedilol and riluzole impacted AD networks without redundancy of drug effects and acromposate and baclofen likewise had non-redundant predicted impact on AD pathophysiology[43]. Computational approaches applied to repurposed drugs may assist in prioritizing which of the many possible therapy combinations are most promising as disease-modifying therapies.

Side effect mining represents an alternative approach to discovering new uses of approved agents. VigiBase®, the World Health Organization's pharmacovigilance database, allows disproportionality data mining that may be useful in repurposing discovery when combined with information regarding the pleiotropic interactions of drugs with their targets[44]. Therapies, for example, that produce cell division might worsen oncology outcomes and benefit NDDs. Pharmacovigilance databases provide comprehensive safety information from real-word use of drugs that may be considered as candidates for treatment of AD/NDD[45].

Computational techniques for the discovery of repurposable agents are sufficiently new that they have not yet led to new therapies for AD/NDD. Experience with successes and failures will allow refinement of the network medicine approaches for development of repurposed agents.

Extrapolations across neurodegenerative disorders. NDDs have many shared neurobiological processes including protein aggregation, inflammation, oxidative injury, neurotransmitter deficits, synaptic dysfunction, lipid dysregulation, and neurodegeneration[46,47]. This suggests that drugs tageting fundamental disease processes present in non-AD NDDs might have a role in treatment of AD. Repurposed agents nominated on this basis with promising outcomes include rasagiline (approved for use in Parkinson's disease), riluzole (approved for use in ALS), and rotigotine (approved for use in Parkinson's disease)[13,14,48]. Rasagiline is a multifunctional agent with transmitter and neuroprotective effects relevant to AD and Parkinson's disease; riluzole is a glutamatergic antagonist and neuroprotective agent promoting neuronal survival in AD and Parkinson's disease; rotigotine as a dopaminergic agonist with transmitter effects on dopaminergic and cholinergic function foundational to cognitive function in AD and Parkinson's disease[49–51]. Cross-disease studies can identify repurposable agents with non-amyloid targets present in the AD/NDDs.

Clinician and patient observations. Most currently used repurposed agents were discovered serendipitously through clinical observation, and this may continue to be a source of preliminary information for repurposing drug discovery. For example, participants in a clinical trial for ALS exploring the possible disease-modifying efficacy of dextromethorphan observed that dextromethorphan decreased symptoms of pseudobulbar affect. This repurposed agent was then combined with repurposed quinidine to establish a new combination agent, Nuedexta®, for the control of pseudobulbar affect in NDDs, multiple sclerosis, cerebrovascular disease, and traumatic brain disorders[52].

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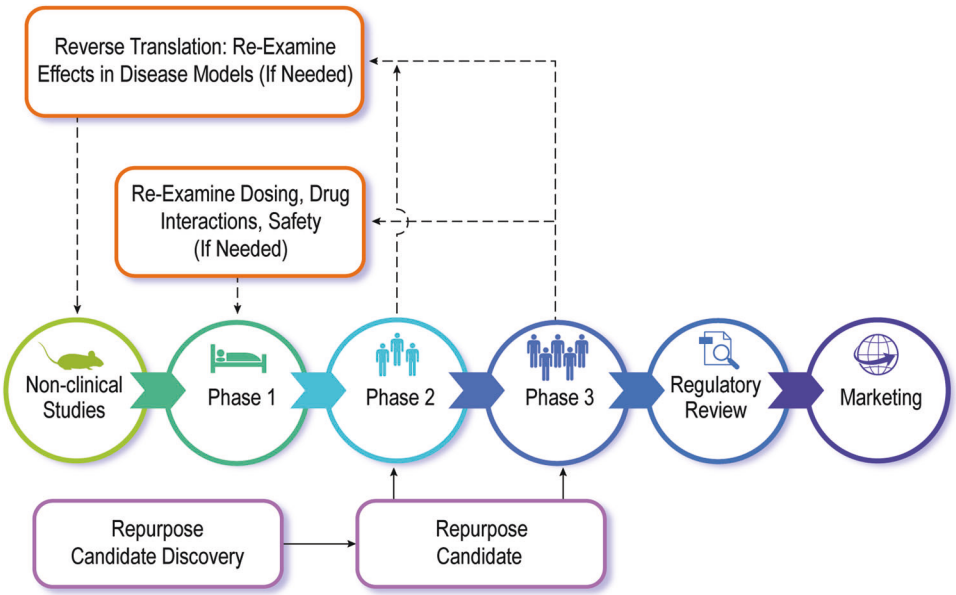

Fig. 1 | The clinical development pathway for a repurposed agent and the alternatives pursued if needed, to characterize the repurposed agent for the new indication. After entering at Phase 2 or Phase 3, reverse translation may be needed to resolve dosing or safety issues in Phase 1 studies or mechanistic questions in non-clinical studies (copyright J Cummings; Illustrator M de la Flor, phD).

Table 2 | Advantages of drug development using repurposed agents

Initiation of development at Phase 2 or Phase 3 without the requirement to repeat Phase 1 or nonclinical studies
Knowledge of dosing information collected in the development program of the agent for the initial indication
Safety information derived from use of the agent to treat the initial indication
Tolerability information derived from use of the agent to treat the initial indication
Lower cost of the test agent, especially if its patent has expired and it has generic status

The dosing, pharmacokinetics, and safety and tolerability of the agent to be repurposed are known. There are advantages to building on this information foundation to launch development campaigns for repurposed agents.
Repurposed agents have been through preclinical development and clinical trials for the original indication.

Assessment of repurposed agents in non-clinical in vitro and in vivo models relevant to AD. An advantage of repurposing as a drug development strategy for AD is that one may avoid non- clinical assessments in animal models and Phase 1 studies in humans since relevant efficacy and toxicity has been determined for the original indication. In some cases, however when a repurposing agent has been nominated through computational or RWD strategies, additional confidence can be gained by conducting reverse translational interrogation of the effects of the drug in animal models or other in vivo approaches (Fig. 1). Fang et al.[31] used multi-omic data, human protein-protein interactome networks and GWAS information to identify repurposing agents for AD. Pioglitazone, an agent used to treat diabetes, emerged as a candidate therapy. In vitro experiments were conducted to show that pioglitazone downregulated glycogen synthase kinase 3-β and cyclin dependent kinase in human microglial cells implicated in AD pathogenesis. Similarly, after showing that sildenafil was associated with a decreased risk for AD using computationally based pharmacoepidemiology data, Fang and colleagues[32] used human induced pluripotent stem cell (iPSC)-derived neurons to show reduced phospho-tau expression relevant to the pathobiology of AD. Williams and colleagues[53] identified transcriptional changes associated with AD in human postmortem and mouse necropsy samples. They screened a library of approved agents to identify 153 drugs opposing AD-type changes in human cell lines. These compounds were then assessed in iPSC-derived cortical neurons to show that 51 of the nominated agents drove expression changes opposite to those characteristic of AD and represented candidates for further study. Similarly, ibudilast was identified as a possible repurposing candidate by Oliveros et al.[54] using a multiscale predictive computational framework. Back-translating to a transgenic rat model, they showed that treated animals had less severe spatial memory deficits and diminished amyloid plaque and tau filament changes compared to untreated transgenic controls. Finally, patients receiving the FDA-approved CREB-binding protein, salsalate, exhibited a decreased incidence of AD observed in large-scale RWD[55]. These observations were supported by showing that salsalate significantly improved cognitive impairment in mouse models of AD non-amyloid mechanisms including reduced tau acetylation[55]. Salsalate had a negative trial in progressive supranuclar palsy[56] and has not been assessed in other NDDs.

Advantages of Repurposing Therapies for AD

There are four main advantages to repurposing as an AD drug development strategy: reduced time required for development with potential earlier advance to market; knowledge of dosing; familiarity with the safety, tolerability, and adverse event profile of the agent; and reduced cost of the test agent and the development program. These advantages can translate into faster, less expensive development programs (Table 2).

Marketed agents have been through non-clinical studies and Phases 1, 2, and 3 for their initial indication. For development as a repurposed treatment for AD/NDD, Phase 1 need not be repeated, and the agent can enter directly into Phase 2 or at Phase 3 depending on the

strength of the available information (Fig. 1). Phase 1 programs that include single ascending dose and multiple ascending dose studies for AD average 2.4 (range 1.4-3.7) years in duration including the recruitment and treatment periods[9]. Planning of the trial before conduct and analysis of the data and discussion of the data with the regulatory authorities add more time to Phase 1. Thus, entering a development program at Phase 2 can save 2.5 to 4 years of development time. The average cost of Phase 1 AD studies has been calculated at $79 million --- the cost avoided by entering a repurposed therapy later in the development cycle[57].

Dosing is a vexing challenge for drug development. Allometric scaling from animal dosing to humans is a typical first step but is often an imperfect guide to age and effective patient doses. In Phase 1, single ascending dose and multiple ascending dose studies lead to the determination of a maximum tolerated dose, dose limiting toxicity, maximum feasible dose (for example, where the volume of administration may set an upper limit), or an upper dose determined by pharmacokinetic or receptor occupancy studies[58]. For repurposed drugs, this dosing experience is available from the original indication for application in Phase 2 and Phase 3 trials for the new indication. While the dosing for the initial indication may differ from that for AD, information available from the initial Phase 1 study is an invaluable guide in dosing considerations.

A major advantage of using repurposed drugs is knowledge of the safety and toxicity of the agent that accrues from development and use of the drug in the initial indication. This information may be collected during Phase 1, Phase 2, and Phase 3 clinical trials as well as from post-marketing experience, EMR review, and RWD[59]. Adverse event prediction can also be pursued with repurposed agents based on the established mechanism of action of the drug[60]. Knowledge of toxicity and safety may contribute to the higher success rate for repurposed agents (30% approval rates across therapeutic areas compared to 1–5% for new molecular entities (NMEs))[61].

Generic repurposed agents generally cost 80-85% less than equivalent branded drugs[62]. Across fields, the cost of bringing a repurposed drug to market has been estimated to be approximately US $300 million, compared to an estimated $2 to $3 billion for an NME[61,63]. Acquiring generic repurposed agents for use in AD/NDD clinical trials is less expensive than acquiring branded agents. If marketing approval were obtained, generic repurposed agents could likely be made available to patients at lower cost compared to novel branded drugs. Global availability and access would be facilitated.

Challenges of repurposing

As noted, knowledge of dosing is an important advantage of repurposed agents, but questions may arise regarding the application of the same doses to the new indications as applied in the original development program. Patients with AD/NDDs may be older than those for whom the original agent was developed (for example, drugs developed for cancer or human immunodeficiency virus therapy (transcriptase inhibitors)). Similarly, questions may arise about drug-drug interactions with treatments commonly used in AD/NDDs or older populations generally. In these cases, Phase 1 trials may be required, reducing the advantages of repurposing (Fig. 1).

Similarly, development of treatments for an original indication may not have required investigation of blood brain barrier (BBB) penetration if the therapeutic target was peripheral. Most therapies of AD require traversing the BBB, Phase 1 studies may be required to establish brain access of the candidate therapy.

Repurposed agents typically comprise 30% of the AD drug development pipeline. Funding of trials of repurposed agents is predominantly by non-pharmaceutical industry sponsors such as the governmental agencies and philanthropies. This differs markedly from trials for NMEs in the AD drug development pipeline where most trials are funded by pharmaceutical companies[9].

The funding pattern of agents in the AD drug development pipeline demonstrates the major challenge associated with developing repurposed agents: lack of funding for advanced stage trials. Repurposed generic agents often languish after completion of Phase 2 for lack of Phase 3 sponsors. The absence of intellectual property protection makes development of generic repurposed agents untenable for pharmaceutical companies since the cost of development cannot be recouped.

Repurposed agents advanced to Phase 3 by industry are usually those with existing patent life and being repurposed from one indication to a closely allied therapeutic area (for example, the development of brexpiprazole for agitation dementia due to AD after successful development for adjunctive therapy for the major depressive disorder, adult schizophrenia, and pediatric schizophrenia). Across therapeutic areas, seventy percent of repurposed agents approved in the US were still on patent and advanced through mechanisms characteristic of NMEs[63].

The cost of Phase 3, regulatory review, scale-up of manufacturing, and development of a marketing campaign differ little for repurposed agents and NMEs. Financial resources for these costs are rarely available in academic medical centers or outside the pharmaceutical industry setting.

If a generic agent was successfully advanced through Phase 3 and to market where it might be positioned with a premium charge to recoup development-related expenses, there is no mechanism for enforcement of use of the repurposed new use generic over the available less expensive generic forumulation[61]. Clinicians and health care systems can substitute generic agents rather than use the new formulations without penalty. In some countries, drug prices are determined centrally and there is no mechanism for price adjustments for new uses[10,11].

In addition to the challenges represented by the lack of intellectual property, investigators have identified other challenges associated with developing repurposed drugs for new therapeutic purposes including lack of access to data from previous trials and lack of transparency regarding clinical trial performance for the original indication[64]. Global databases on drugs and drug effects have been championed as one solution to the problem of lack of data availability[65].

Strategies for advancing generic agents to late-stage trials

Legislation is needed to provide incentives for development of generic drugs as marketable treatments for AD (Table 3). In the US and Europe, statutes and regulatory policies have led to the development of many new drug therapies for rare diseases, and similar legislative strategies including tax incentives and market exclusivity might be used to enhance interest in repurposed drug development[66]. Legislation can be advanced to incentivize development of repurposed generics for serious illnesses for which there are insufficient alternative therapies such as AD/NDDs. Attaching payment to the indication for which the repurposed agent is approved would allow revenue generation from sales for the new use of the agent. An innovation surcharge could be collected from generic wholesalers when a new use is involved[67]. Other solutions might include enabling generic companies to have larger pharmaceutical enterprises advance Phase 3 studies of their generic repurposed agents in return for fees collected from the generic developer if the development program is successful[68]. Many nations and regions are re-examining their policies regarding market access for repurposed agents including Europe, Sweden, United Kingdom, and Australia[69]. Japan has a novel approval mechanism for off label use of drugs applicable to repurposed agents and has considered an approach to approval of repurposed drugs based on demonstration of safety in the population treated by the new use[70]. In the European Union, a Virtual Repurposing Observatory group has been established to conduct a pilot project comprised of support from not-for-profit

Table 3 | Financial, legislative, and scientific strategies for advancing generic agents

Legislative strategies	Provision of period of exclusivity for generic repurposed agents
	Tax incentives for scientific development of new uses devoted to neurodegenerative disorders
	Legislation to require public and private insurers to reimburse the new use of generics with established efficacy and safety for a neurodegenerative disorder
Regulatory strategies	Waiver of Prescription Drug User Fee Act (PDUFA) fees
	Establishment of rapid communication channels with regulatory agencies
	Rapid review and expert input by regulatory authorities during the development process
Financial strategies	Innovation surcharge
	Social impact investing
	Mega-fund creation
	Crowdsourcing
	Motivational prizes
	Advocacy collaboration
	Philanthropy or venture philanthropy
Scientific strategies	New formulations (patch, sublingual, etc)
	New dosing approaches
	Novel combination therapies
	Prodrug identification and development
	Medicinal chemistry approaches to create new molecular entities that may have the benefits observed in trials of generic agents

A variety of strategies spanning legislative, regulatory and scientific approaches can assist in advancing repurposed agents. Innovative financial tools may help to fund trials of repurposed agents where intellectual property protection is limited and conventional funding streams are unavailable.
There are hurdles to advancing repurposed agents as treatments for neurodegenerative disorders.

stakeholders to generate data on new therapeutic uses of established medicines. Information from the Observatory could help transform the process for approval of repurposed agents[71].

Social finance strategies might also be considered, allowing redirection of taxes to financing of late-stage development of repurposed agents for serious illnesses. Companies created to support late-phase development and marketing based on tax incentives and funding from philanthropy and advocacy groups could help address the current roadblocks to getting repurposed drugs to market. Prizes and rewards could be used to help motivate payers/insurance companies, healthcare systems, or manufacturers to conduct new use research for off-patent generic agents with promising applications to AD/NDDs[11]. Megafunds employing dynamic leverage strategies have been championed for orphan drug candidates and could be applied to repurposed drug development[72]. Crowdfunding, social impact investing, and public-private partnerships are additional avenues for funding to be explored[10,11,73]. In the US, legislation regarding insurance companies and the Center for Medicare and Medicaid Services might allow collection of a premium on drug costs when documentation of prescribing for the new indication is available (Table 3). These proposed solutions await testing across therapeutic areas.

Current US legislative trends make repurposing for AD more difficult. In the US, congress seeks to ensure public access to medications and to limit "ever-greening" by pharmaceutical companies through patent "thickets" and other means of limiting competition and delaying the marketing of generics[74]. These laws have the unintended consequence of making the new use of generics more difficult. These reverse incentives can be identified and modified.

Financial strategies can be complemented by scientific initiatives directed at patent and intellectual property protection (Table 3). Composition of matter patents have typically expired on generic compounds but use patents, changes in formulation, new dosing forms, deuteration of the parent agent, and development of combination therapies with other agents can capture substantive intellectual property protection attractive to large companies or investors[68]. Use patents may be pursued but if the new application has been mentioned in the literature, then the use is "obvious" and not patentable[63,75]. Discovery or development of pro-drugs that are metabolically converted to the generic agent may be an acceptable development pathway dependent on showing equivalent bioavailability of the drug from the pro-drug[76].

Regulatory strategies could be applied to support new uses of repurposed generic agents. Tax credits can be awarded for research activities. In the US, market exclusivity can be granted, and the Prescription Drug User Fee Act (PDUFA) payment requirements (currently approximately $3 million for a new drug) can be waived.

If a sponsor is developing agents for diseases with major unmet needs such as AD/NDDs, they may be eligible for special FDA designations including Fast Track, Priority Review, and Breakthrough Therapy[77]. The US 21st Century Cures Act encouraged the FDA to use nontraditional clinical trials, innovative data analytic methods, real world evidence, observational studies, biomarkers, and surrogate endpoints as the basis of drug approval assuming that standards for safety and efficacy are met[77]. These regulatory strategies could be leveraged to support development of repurposed agents for AD/NDDs.

Multi-stakeholder collaborations can provide a platform for consideration of repurposing as an AD/NDD drug development pathway with identification of viable scientific and economic strategies. Patients, care partners, clinicians, trialists, pharmaceutical and biotechnology industries, federal agencies, advocacy groups, investors, and philanthropists have a common interest in advancing treatments for AD/NDD as quickly as possible.

A strategy relevant to companies requiring robust intellectual property protection is to use repurposed generics to identify drug structures and target pathways that can then be exploited by NMEs (Table 3). These drugs require long term commitment to progress through non-clinical studies, Phase 1, Phase 2, and Phase 3 to regulatory review, but experience with repurposed agents can be an important starting point for the development process[78].

Repurposed drugs are an essential aspect of the drug development ecosystem

Investment of time, funding, and other resources in repurposed drug development could be regarded as misguided given the low likelihood of successful development of a marketable compound. However, clinical trials devoted to repurposed agents are essential to the drug development ecosystem for AD/NDD therapies (Table 4).

Most generic drug development does not occur in industry-sponsored studies and depends on non-industry, mostly academic, settings. Academic Medical Centers (AMCs) are engines of innovation and are positioned to generate new data and develop new technologies that can be used by both the biopharmaceutical industry and academic enterprises to develop new therapies. Pharmaceutical companies are risk averse in adopting new approaches, strategies, technologies, and measures, since the performance of innovations in trials is not established, and failures associated with their use can jeopardize the outcome of costly development programs. AMCs are not constrained by these pressures.

The conduct of Phase 2 proof-of-concept studies with repurposed drugs in AMCs leads to the establishment of a clinical trial infrastructure, and these academic sites comprise essential aspects of the US and global drug development ecosystem[79]. Personnel required at the sites and applicable to industry-sponsored as well as repurposed

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Table 4 | Aspects of the drug development ecosystem that are supported by clinical trials of repurposed agents

Infrastructure development, particularly in academic medical centers	Trial site venue
	Imaging (magnetic resonance imaging, molecular)
	Biomarker collection
	Participant engagement and education
Work force development	Training trialists for academics and industry
	Site principal investigators advanced from junior investigators
	Research nurses
	Psychometricians
	Research coordinators and assistants
	Regulatory personnel
	Budgetary experts
Revenue generation	Experimental approaches to novel recruitment and retention strategies, especially as they apply to minority populations and under-represented groups
	Proof of concept for intervention in an identified disease pathway
	Proof of concept for a specific mechanism for disease treatment
	Proof of concept for possible combination therapies
	Novel clinical outcome assessment development
	Novel brain imaging development
	Novel biomarker development
	Novel digital device development
	Development of new trial designs and analyses

Repurposed agents are rarely advanced to late-stage Phase 3 clinical trials, and their principal role in the drug development ecosystem is to advance new knowledge and new technologies. Innovations often arise and are tested in academic medical centers and can then be made available to pharmaceutical and biotechnology companies to advance drug development and accelerate the availability of new treatments for patients. Trials of repurposed agents provide a platform for discovering potential therapeutics and advancing technological innovations for clinical trials, building infrastructure, and providing workforce development.

drug trials are in place. In the US, AMC trial facilities may be supported in part by Clinical and Translational Science Awards (CTSAs) and similar funding may be available in other countries[80]. In LMICs, trial infrastructure enhances science education, advances the understanding of the scientific approach to aging and diseases of older individuals, and creates opportunities for international collaboration. Conducting trials in LMIC countries is an important step toward achieving global equity in health care and medical research.

The workforce of the biopharmaceutical industry is created in academic environments dependent on repurposing agents[81]. Hands-on clinical trial experience with repurposed agents and interacting with the biopharmaceutical industry personnel influence career choices.

A major deficiency of most AD clinical trials is the lack of adequate representation of minority ethnic and racial participants. In US trials, participants from these under-represented groups often comprise 5% or less of the trial population even though they comprise up to 30% of the relevant populations and are at increased risk for AD compared to White individuals[82]. AMCs are poised to address this important challenge. Community outreach is a critical component of academic clinical trial units, and strategies for engaging minoritized communities can be developed through culturally informed strategies. Achieving representative recruitment at this foundational level across a network of AMC clinical trial sites will result in more adequate representation of minority populations in clinical trials of both repurposed drugs and NMEs.

AMCs have been the source of most outcome measures used in clinical trials and adopted by pharmaceutical companies and regulatory agencies. These tools evolve in academic settings because of the research experiences --- often with trials of repurposed drugs --- of the creators. Widely used clinical outcome assessments in AD clinical trials such as the Mini-Mental State Examination (MMSE)[83], Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog)[84], Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS ADL) scale[85], Neuropsychiatric Inventory (NPI)[86], and Clinical Dementia Rating (CDR)[87] are examples of clinical assessments that originated in academic centers and have become standards in clinical trials. Newer types of clinical outcome assessments evolving in AMCs and gradually being integrated into clinical trials include neuropsychological instruments for prevention trials, computerized cognitive assessments, online assessments, and digital biomarkers. One goal of these programs is to show that the new strategy or technology is "fit for purpose" for use in clinical studies and can be assimilated into industry trials.

Biomarkers are transforming AD drug development, and these new biological measurement approaches have originated in AMCs or startup companies with their roots in academia. Amyloid positron emission tomography (PET), tau PET, and advanced magnetic resonance imaging (MRI)[88,89] are university-derived, and the revolution in cerebrospinal fluid (CSF) and blood-based biomarkers reflects a critically important contribution of AMCs to the drug development and clinical trial process[90].

Recognizing the importance of the many roles that repurposed agents and trials of these agents play in the drug development ecosystem allows them to be developed with greater intentionality. Infrastructure creation and sustainability, workforce development, clinical outcome measure innovation, and biomarker discovery can be embedded in trial programs for repurposed agents.

There are too few trial sites in LMICs, and expansion of the global trial network is needed to accelerate patient recruitment and hasten the development of critically needed new therapies. Global repurposing trials have many benefits including developing local experts for AD/NDD diagnosis, improving local understanding age-related disorders, increasing expertise at all levels of the workforce working with older individuals, and enhancing the contribution of trial sites in LMICs to global AD science. The drug development ecosystem including trials of repurposed agents is the support structure that, viewed longitudinally and globally, produces the agents and innovations critical to advancing urgently needed treatments.

Conclusion

Repurposing is an efficient drug development strategy that can advance new therapies more quickly and with less expense than development of NMEs. New computational strategies, in vitro and in vivo experimental studies, and pharmacoepidemiologic investigations, as well as clinical observations can be used to generate data for candidate selection. The lack of intellectual property protection and the limited interest of pharmaceutical sponsors in developing generic repurposed agents pose substantial challenges to advancing repurposed agents to late-stage development. Scientific, legislative, and regulatory strategies are required to incentivize development of repurposed agents and allow them to be advanced to Phase 3 and possible market approval.

Trials of repurposed agents are an essential part of the global drug development ecosystem for AD/NDDs. These trials lead to the creation of new outcomes, design strategies, and biomarkers while advancing infrastructure, education, and community engagement. More trial sites are needed to accelerate drug development, and the ecosystem can be a means of enhancing collaboration among global sites and regions. A global trial network can accelerate drug development for AD/NDDs and enhance the lives of older individuals worldwide.

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Author contributions

Each other has made substantial contributions to this article in terms of its conception (J.L.C., A.S., F.C.), design (J.C., Y.Z., A.S., D.C., R.T., J.R., F.C.), data acquisition (J.L.C., Y.Z., A.S., D.C., R.T., J.F., F.C.), data analysis (J.L.C., A.S., F.C.), or data interpretation (J.C., Y.Z., A.S., D.C., R.T., J.R., F.C.). All authors have reviewed the drafts and participated substantively in revisions (J.C., Y.Z., A.S., D.C., R.T., J.R., F.C.). All authors have approved the submitted version (J.C., Y.Z., A.S., D.C., R.T., J.R., F.C.). All authors have agreed to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated, resolved, and the resolution documented in the literature (J.C., Y.Z., A.S., D.C., R.T., J.R., F.C.).

Competing interests

J.C. has provided consultation to Acadia, Acumen, ALZpath, Axsome Artery, Biogen, Biohaven, Bristol-Myers Squib, Eisai, Fosun, GAP Foundation, Janssen, Karuna, Kinoxis, Lighthouse, Lilly, Lundbeck, LSP/eqt, Merck, MoCA Cognition, New Amsterdam, Novo Nordisk, Optoceutics, Otsuka, Oxford Brain Diagnostics, Praxis, Prothena, ReMYND, Roche, Scottish Brain Sciences, Signant Health, Simcere, sinaptica, TrueBinding, and Vaxxinity pharmaceutical, assessment, and investment companies. J.C. is the owner of the Neuropsychiatric Inventory. Y.Z., A.S., D.C., R.T.-K., J.F., and F.C. declare no competing interests.

Additional information

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