A Review: Treatment of Alzheimer's Disease Discovered in Repurposed Agents

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Key Words

Dementia · Therapeutics · Pharmacology, clinical · Clinical trials · Drug therapy · Drug effects · Amyloid · Amyloid β -peptides · Tau proteins · Tauopathies

Abstract

Background/Aims: Many compounds that have already been approved for alternate diagnoses have been studied in relation to Alzheimer's disease (AD). The purpose of this review is to summarize these studies and discuss the rationale and benefits of repurposing drugs for AD treatment. **Methods:** Studies of drugs related to AD treatment that were relevant to a disease-modifying mechanism of action (MOA) and are already approved by the Food and Drug Administration for non-AD diagnoses were collected from PubMed. **Results:** Many drugs already approved for the treatment of other diseases have been studied in relation to AD treatment. Numerous drugs with known toxicity profiles have the potential to be repurposed as a treatment for AD. **Conclusion:** Known MOA, toxicology, and pharmacodynamic profiles would accelerate the process and increase the odds of finding a more timely disease-modifying treatment for AD.

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Introduction

Alzheimer's disease (AD) is a progressive fatal degenerative disease of the brain that is assuming epidemic proportions as the world's population ages. It is currently predicted that the number of affected individuals will reach 100 million by 2050 if means of ameliorating the disease are not found [1]. There is an urgent need to find interventions that will prevent, delay the onset, slow the progression, or improve the symptoms of AD. Academic laboratories, biotechnology companies, and pharmaceutical companies are pursuing new targets, identifying and optimizing compounds, and conducting clinical trials to attempt

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to find new treatments for AD. The difficulty of advancing the AD treatment agenda is attested by the absence of any new approved therapies since 2004 [2].

Most current efforts to find new therapies for AD are directed at identifying new chemical entities that affect the underlying disease process and produce a drug-placebo difference in clinical and biomarker outcomes. Another rich source of compounds with potential disease-modifying effects are drugs that are approved for other indications but which may interact with AD-related pathophysiological pathways through mechanisms unrelated to their original therapeutic intention. A growing literature documents the AD-related effects of approved compounds. Advancing these compounds may have advantages in terms of reducing development time, and repurposing as a means of advancing new therapies has been emphasized in the agenda of the National Center for Advancing Translational Science [3]. This review discusses the approach to using repurposed compounds and describes the literature addressing the effects on AD of approved agents.

Repurposing as an Alzheimer's Disease Drug Development Strategy

Repurposing refers to the development of new uses for existing or abandoned pharmaceuticals [4]. The new use may be on target and related to the original mechanism of action (MOA) or off target and related to a new MOA [5]. Repurposing has gone by a variety of names including repositioning, reprofiling, therapeutic switching, and retasking [5]. Repurposing is to be distinguished from life cycle management involving new formulations, new doses, and extended indications closely related to the original approved indication (e.g. extension of the indication from mild-to-moderate to severe AD). Abandoned drugs are those that have been stopped in the course of development prior to approval for reasons other than safety [5]. There are many such compounds but knowledge of them is proprietary, the reasons for discontinuation are not generally published, and a comprehensive list of these agents is not publicly available. This review addresses approved agents with effects on AD, not abandoned agents.

Up to 30% of compounds have new uses suggested by phenotypic screens that examine pharmacological activity similar to that of established treatments, an indication of the high rate of uncharacterized actions of approved agents [2]. Ninety percent of the new activity is related to the original MOA while 10% suggests the presence of activity on targets not previously known to be impacted by the agent. Screening for new effects may involve a variety of high and medium throughput approaches including phenotypic screens, in silico approaches, gene expression profiling with construction of drug response communities, self-organizing maps and networks of drug effects, clinical data mining, proteomics, animal models, and traditional high throughput assays for established target mechanisms [6–10]. The increasing use of the electronic medical record may facilitate the discovery of unanticipated benefits of drug therapy as well as the characterization of adverse events. Electronic medical records establish a means of high-throughput screening in humans [11, 12]. Effects on biomarkers may also support new MOAs for existing agents [13].

There are many potential advantages to advancing repurposed agents in drug development programs. Importantly, preclinical and clinical toxicities have been established for the approved doses. Fifty percent of agents fail in development for toxicity and pharmacokinetic reasons, and repurposed compounds can avoid these risks [14]. Pharmacokinetic (absorption, distribution, metabolism, excretion, bioavailability), formulation, and manufacturing issues have been resolved. Compounds that have been shown to be effective in another therapeutic setting will have gone through the optimization process and have the molecular features required for druggability and manufacturing. Repurposing may allow a company to recover an otherwise lost investment of an abandoned compound and to derive new income from an agent found to have a new target and new indication.

Many approved agents have been observed to have effects relevant to AD. These compounds offer repurposing opportunities that may help accelerate the development of new treatments for AD. These agents and the classes of observation linking them to AD are presented here.

Methods

A comprehensive review of the literature was conducted to ascertain compounds currently approved by the United States Food and Drug Administration (FDA) for non-dementia-related indications that may have an impact on the treatment of AD. PubMed was searched using the key words ‘Alzheimer’s disease’ and ‘treatment’ followed by classes of medications (e.g. ‘antibiotics’). Compounds discovered by this preliminary search were then explored using the key words ‘Alzheimer’s disease’ and ‘treatment’, followed by the individual compound (e.g. doxycycline). These articles were reviewed for content, and references were further reviewed if not captured via the aforementioned search queries. Compounds were included only if deemed to have a potential disease-modifying effect; symptomatic treatments were not considered for review. Potential disease-modifying factors included mechanisms associated with disruption of amyloid or tau pathology, neuroprotection, anti-inflammation, and/or neurogenesis. Compounds with unknown MOAs were included if they exhibited relevance to AD based upon epidemiological data. Nutraceutical and herbal remedies were not included.

The above data were collected, analyzed, and organized based on the source and level of evidence. Five sources of evidence were considered: (1) data based on in vitro studies, (2) data based on animal models, (3) data based on epidemiological or observational studies in humans, and (4) data based on multiple lines of evidence (tables 1–4).

Results

Anticancer Agents

Imatinib

Imatinib, currently approved by the FDA for the treatment of chronic myelogenous leukemia and gastrointestinal stromal tumors, targets the Bcr-Abl complex and binds to the ATP-binding site of c-ABL and other tyrosine kinases [15]. Several in vitro and in vivo studies have suggested that it may have a therapeutic effect in AD via two possible mechanisms (table 4). Studies have demonstrated reduced β -amyloid ($A\beta$) production in AD models treated with imatinib [16–18]. In addition to reducing the amount of $A\beta$ deposits, imatinib also demonstrates neuroprotective effects. Though mild cardiotoxicity has been described, there have been no major adverse effects reported with imatinib’s use in humans [19]. The primary obstacle to its use in the treatment of AD is its low cerebral penetration as it is readily removed from the central nervous system by glycoprotein-p [19].

Paclitaxel

Paclitaxel is a microtubule-stabilizing agent that is FDA approved for the treatment of ovarian carcinoma, breast cancer, non-small-cell lung cancer, and AIDS-related Kaposi’s sarcoma. Studies have demonstrated its treatment potential in AD and tauopathies (table 1). Phosphorylated tau (p-tau) reduces tau’s ability to bind microtubules and enhances fibrilization. Similar to imatinib, paclitaxel is a glycoprotein-p substrate and achieves poor central nervous system penetration [20]. Paclitaxel’s putative effect in neurodegenerative illnesses is related to microtubule stabilization, reduction of tau phosphorylation, improvement of tau function, and inhibition of $A\beta$ -induced activation of the cystolic cdk5-p25 complex and calpain [20–22].

Table 1. Agents with effects demonstrated in cell and tissue models relevant to AD

Agent	Current use	AD-related observation
Paclitaxel	Oncology	Neuroprotective Reduces tau phosphorylation
Thalidomide	Oncology	Neuroprotective Anti-inflammatory Antiangiogenic
Azithromycin	Antimicrobial	Alters APP processing
Acyclovir, penciclovir, and foscarnet	Antivirals	Reduces A β accumulation Reduces p-tau accumulation
Amphotericin B	Antimicrobial	Possibly delays A β fibril formation
Exenatide	Diabetes	Neuroprotective Reduces tau hyperphosphorylation
Isradipine	Antihypertensive	Neuroprotective
Hydroxychloroquine	Antimicrobial Rheumatological diseases	Anti-inflammatory
Trehalose	Glucose disaccharide	Promotes formation of α -helical conformation of A β peptide
Pramipexole	PD	Neuroprotective Antioxidant

APP = Amyloid precursor protein; A β = β -amyloid; p-tau = phosphorylated tau; PD = Parkinson's disease.

Table 2. Agents with effects demonstrated in animal models relevant to AD

Agent	Current use	AD-related observation
Erythromycin	Antimicrobial	Alters APP processing Possibly neuroprotective
Tetracycline	Antimicrobial	Reduces A β aggregation Lowers oxidative stress
Lixisenatide	Diabetes	Promotes neurogenesis
Amlodipine	Antihypertensive	Inhibits A β production
Olmesartan	Antihypertensive	Neuroprotective
Nortriptyline	Tricyclic anti-depressant	Neuroprotective
Desvenlafaxine	SNRI	Decreases cerebral A β levels
Risperidone	Antipsychotic	Neuroprotective
Quetiapine	Antipsychotic	Antioxidant Neuroprotective
Olanzapine	Antipsychotic	Antioxidant Neuroprotective Increases neurogenesis of dentate gyrus
Zileuton	Antiasthmatic	Inhibits A β production and deposition

APP = Amyloid precursor protein; A β = β -amyloid; SNRI = serotonin and norepinephrine re-uptake inhibitor.

Table 3. Agents with epidemiological and/or human biological observations demonstrated in humans relevant to AD

Agent	Current use	AD-related observation
Angiotensin-converting enzyme inhibitors	Antihypertensives	Decrease the incidence of AD, vascular, and mixed dementia
Enalapril	Antihypertensive	Decreases incidence of dementia, including AD, in patients with isolated systolic hypertension
Angiotensin receptor blockers	Antihypertensives	Decrease the incidence of AD, vascular, and mixed dementia
β-Blockers	Antihypertensives	Decrease the incidence of dementia
Hydrochloro-thiazide	Antihypertensives	Decrease the incidence of dementia, including AD, in patients with isolated systolic hypertension

Thalidomide

Originally used as a sedative, thalidomide is perhaps most known for its teratogenic effects. The compound is currently approved for treatment of moderate to severe erythema nodosum leprosum and multiple myeloma [23]. Thalidomide's potential as a treatment for AD was demonstrated in an in vitro study in which it blocked vascular changes including endothelial cell proliferation, angiogenesis, and breakdown of the blood-brain barrier (BBB; table 1) [23]. In addition to affecting cerebral microvasculature, thalidomide also blocked astrogliosis and reduced hippocampal neuronal loss via inhibition of tumor necrosis factor- α . Thus, thalidomide may have anti-AD effects via anti-inflammatory, antiangiogenic, and neuroprotective mechanisms.

Bexarotene

Bexarotene, a compound currently used to treat cutaneous T-cell lymphomas, has shown promise in mouse models of AD (table 4). Bexarotene's putative MOA is retinoid X receptor agonism, which is hypothesized to affect the induction of apolipoprotein E expression by affecting liver X receptor-retinoid X receptor complexes [24]. In vitro results indicate peroxisome proliferator-activated receptor- γ , liver X receptor, and apolipoprotein-E-dependent degradation of A β (1–42) with bexarotene treatment. Bexarotene is a good candidate for further drug development in AD treatment given its high BBB permeability and current safety profile.

Antimicrobials

Macrolide Antibiotics

Two macrolide antibiotics currently used to treat various infectious diseases have been studied in AD models. In an in vitro study examining amyloid precursor protein (APP) processing, several compounds known to affect the 5'-untranslated region of APP mRNA were studied (table 1) [25]. Azithromycin altered APP processing by inhibiting APP 5'-untranslated region conferred translation in addition to altering APP cleavage. An analog of azithromycin, erythromycin, was also investigated in a similar study using an AD mouse model [26]. Like azithromycin, erythromycin altered APP processing resulting in reduced cerebral levels of A β (1–42) without affecting A β (1–40) levels (table 2). Erythromycin may have neuroprotective effects via induction of the expression of a 7-kDa APP C-terminal fragment, which may increase expression of neuroprotective target genes.

Table 4. Agents with multiple types of supporting data relevant to AD

Agent	Current use	Sources of evidence	AD-related observation
Imatinib	Oncology	In vitro Animal models	Reduced A β production Neuroprotective
Bexarotene	Oncology	In vitro Animal models	Increases A β clearance
Clioquinol	Antimicrobial	Animal models Clinical trials	Metal protein-attenuating compound
Doxycycline	Antimicrobial	Animal models Clinical trial	Reduced A β fibrillation Neuroprotective
Minocycline	Antimicrobial	In vitro Animal models	Neuroprotective
Rifampin	Antimicrobial	In vitro Clinical trial	Reduced A β deposition and fibrillation Neuroprotective
Dapsone	Antimicrobial	In vitro Human observational studies	Possibly decreases amyloid deposition
Metformin	Diabetes	In vitro Animal models	Reduced tau hyperphosphorylation Prevented AD pathology in insulin-resistant model
Rosiglitazone	Diabetes	In vitro Animal models Clinical trials	Anti-inflammatory Reduced A β oligomers
Pioglitazone	Diabetes	Animal models Clinical trials	Reduced oxidative stress Normalizes cerebrovascular blood flow Anti-inflammatory
Liraglutide	Diabetes	In vitro Animal models	Neuroprotective Reduced A β oligomers Anti-inflammatory
Insulin	Diabetes	In vitro Animal models Clinical trials	Reduced A β production Increases A β clearance Neuroprotective
Statins	Cholesterol-lowering agents	In vitro Animal models Clinical trials	Lowers β - and γ -secretase APP processing leading to reduced A β Possibly increases nonamyloidogenic α -secretase APP-processing pathway
Nilvadipine	Antihypertensive	In vitro Animal models Clinical trials	Restores regional cerebral blood flow Inhibits A β production Increases A β clearance Neuroprotective
Nitrendipine	Antihypertensive	In vitro Animal models Clinical trials	Restores regional cerebral blood flow Increases A β clearance
Nimodipine	Antihypertensive	In vitro Clinical trial	Neuroprotective
Verapamil	Antihypertensive	In vitro Animal models	Neuroprotective Reduces A β (1–40) oligomers
Valsartan	Antihypertensive	In vivo Animal models	Prevents A β oligomerization
Valproic acid	Antiepileptic	In vitro Animal models	Anti-inflammatory Enhances phagocytosis of A β Inhibits GSK-3 β -mediated γ -secretase cleavage of APP
Amitriptyline	Tricyclic antidepressant	In vitro Animal models	Increases hippocampal BDNF and dentate gyrus neurogenesis Neuroprotective Decreases cerebral levels of A β (1–42)
Citalopram	SSRI	Animal models Human epidemiological studies	Decreases cerebral A β levels and amyloid plaques

Table 4 (continued)

Agent	Current use	Sources of evidence	AD-related observation
Fluoxetine	SSRI	Animal models Human epidemiological studies	Increases neurogenesis of dentate gyrus Antioxidant Possibly decreases amyloid plaques
Paroxetine	SSRI	Animal models Human epidemiological studies	Reduces A β levels Reduces p-tau levels Increases hippocampal neurogenesis Possibly decreases amyloid plaques
Sertraline	SSRI	Animal models Human epidemiological studies	Increases hippocampal BDNF and neurogenesis Possibly decreases amyloid plaques
Deprenyl (selegiline)	MAOI	In vitro Animal models	Neuroprotective Prevents DNA fragmentation Stimulates α -secretase cleavage of APP
Rasagiline	MAOI	In vitro Animal models	Neuroprotective Prevents DNA fragmentation Stimulates α -secretase cleavage of APP
Ladostigil	MAOI	In vitro Animal models	Neuroprotective Prevents DNA fragmentation Stimulates α -secretase cleavage of APP Inhibits acetyl- and butyrylcholinesterase
Lithium	Mood stabilizer	In vitro Animal models Clinical trials	Decreases A β production Inhibits γ -secretase cleavage of APP Inhibits GSK-3 β -mediated tau phosphorylation Neuroprotective Decreases CSF p-tau Improves cognition
Nonsteroidal anti-inflammatory drugs	Analgesic	In vitro Animal models Human epidemiological studies	Anti-inflammatory Antioxidant Reduces A β (1–42)
Colchicine	Gout treatment	In vitro Human epidemiological studies	Inhibits internalization of membrane-bound APP Anti-inflammatory
IVIG	Autoimmune-mediated illnesses	Animal models Human epidemiological studies	Increases clearance of cerebral A β
Apomorphine	PD	In vitro Animal models Biological observation in humans	Stimulates degradation of A β
Dantrolene	Toxicities	In vitro Animal models	Neuroprotective
Methylene blue	Toxicities	In vitro Animal models	Antioxidant Facilitates tau degradation and clearance Promotes autophagy Reduces A β levels
Nicotine	Smoking cessation	In vitro Animal models Clinical trials	Promotes nonamyloidogenic pathway Neuroprotective

A β = β -Amyloid; APP = amyloid precursor protein; GSK = glycogen synthase kinase; BDNF = brain-derived neurotrophic factor; SSRI = selective serotonin reuptake inhibitor; MAOI = monoamine oxidase inhibitor; CSF = cerebrospinal fluid; p-tau = phosphorylated tau; IVIG = intravenous immunoglobulin; PD = Parkinson's disease.

Tetracyclines

Several studies have examined the use of tetracyclines in AD mouse models and have found a reduction in A β aggregate formation, reduced resistance of A β (1–42) to trypsin digestion, and an increase in disassembly of preformed fibrils (table 2) [27–29]. These effects were dose dependent and specific to tetracyclines as opposed to antibiotics in general [28, 29]. The most recent study also demonstrated lowered oxidative stress in tetracycline-treated animals, suggesting a multifactorial MOA [29].

A very commonly used tetracycline derivative, doxycycline, has been studied as well. An AD fly model demonstrated neuroprotection from A β toxicity and prevention of A β fibrilization that was dose dependent (table 4) [30]. A randomized, placebo-controlled trial using doxycycline 200 mg and rifampin 300 mg orally daily for 3 months in subjects with mild to moderately severe AD was conducted in Canada [31]. Treated subjects demonstrated less decline on the Standardized Alzheimer's Disease Assessment Scale Cognitive Subscale at 6 months, but there were no differences between treatment and placebo groups at 3 and 12 months. However, no beneficial effects on cognition or functioning were detected when doxycycline was used alone or in combination with rifampin in a recent study [32]. A different tetracycline derivative, minocycline, has demonstrated neuroprotective effects related to the inhibition of microglial activation (table 4) [33–40].

Antiviral Compounds

One in vitro study has examined the effects of antiviral medications in AD. Acyclovir, penciclovir, and foscarnet were found to reduce A β and p-tau levels in AD cell models (table 1) [41].

Clioquinol

Clioquinol (CQ) is a hydroxyquinoline with antifungal and antiprotozoan properties that is still used in some topical preparations to treat skin infections. In transgenic mouse models of AD, CQ was found to reverse working memory impairments, reduce amyloid plaques in the cortex and hippocampus, and attenuate astrogliosis (table 4) [42]. Treatment with CQ was also associated with altered biometal levels within the brain (copper, zinc, and iron) and its distribution within the brain mirrored areas implicated in memory and learning. These observations led to a clinical trial using CQ. Thirty-six subjects with moderately severe AD were included in a phase II randomized double-blind trial using CQ [43]. After 36 weeks, a treatment effect was observed in the more clinically severe cases. Plasma A β (1–42) levels decreased in the CQ group and increased in the placebo group. Plasma zinc levels also increased in the CQ group, but copper levels remained unchanged. Overall, CQ was well tolerated by subjects at a maximum oral dose of 375 mg twice per day.

Rifampin

Rifampin is an antimicrobial within the rifamycin family that is commonly used to treat *Mycobacterium* infections. In vitro studies have detected dose-dependent reductions of A β fibrils in AD cells treated with rifampin possibly due to decreased production and increased clearance of A β (table 4) [28, 44, 45]. Two clinical trials of doxycycline in combination with rifampin have also been conducted as previously discussed [31, 32].

Amphotericin B

Amphotericin B is an antifungal medication that has several known toxicities including multiorgan failure and potentially death that would likely limit its use as a treatment for AD. In vitro studies have been mixed regarding its possible use in AD. One study found that amphotericin B delayed A β fibril formation, whereas another study did not (table 1) [46, 47].

Dapsone

Dapsone is used to treat leprosy and received attention in the 1990s as a possible treatment for AD. The first suggestion that dapsone may be beneficial in dementia came from a Japanese epidemiology study that detected a decreased prevalence of dementia in leprosy patients 65 years of age or older who had been treated with dapsone and related medications compared to those who had never been treated (table 4) [48]. A neuropathological case series of leprosy patients detected the absence of senile plaques but the expected levels of neurofibrillary tangles compared to the general population [49]. The following year, a similar study refuted these results by not finding any differences in senile plaques between leprosy patients and controls [50]. A conflicting study found less A β deposition but more abnormal tau deposition in the brains of leprosy patients than expected raising the question of whether the disease itself might be a protective factor against amyloid deposition [51]. This hypothesis is further strengthened by similar instances of AD in lepromatous and tuberculoid patients despite differences in the percentage of patients that underwent drug treatments in these two groups [52, 53].

Diabetes-Related Agents

Metformin

Metformin is a biguanide compound used to treat type II diabetes mellitus (DM II). Experimental observations of this agent in AD models have produced mixed results. When administered alone, metformin increased the generation of A β species by upregulating β -secretase 1, however; A β levels were reduced when it was administered with insulin (table 4) [54]. When administered in an insulin-resistant neuron model, metformin prevented neuropathological and molecular features of AD [55]. Another study demonstrated reduced tau hyperphosphorylation with plasma concentrations of metformin that were much lower than what is typically used to treat DM II [56].

Peroxisome Proliferator-Activated Receptor- γ Agonists

Two peroxisome proliferator-activated receptor- γ agonists used to treat DM II, rosiglitazone and pioglitazone, have been studied in relation to AD treatment (table 4). In vitro studies have shown synergistic neuroprotective effects when rosiglitazone is administered with insulin, whereas partial neuroprotection occurs with rosiglitazone treatment alone [57]. Several animal model studies of AD have demonstrated reduced cognitive impairment, A β oligomers, and inflammation with rosiglitazone treatment [58–62]. Rosiglitazone's anti-AD effects are independent of its effect on glucose regulation [59]. Several randomized controlled trials have investigated the effect of rosiglitazone on amnesic mild cognitive impairment (aMCI) and AD subjects with mixed results. One study revealed improved cognition in the treatment group without changes in plasma A β levels and another showed improved cognition in non-APOE-4 carriers [63, 64]. These results were not replicated in additional trials, even when subjects were stratified by APOE-4 allele status [65–67].

Another peroxisome proliferator-activated receptor- γ agonist, pioglitazone, has also been studied in animal models and randomized controlled trials (table 4). These studies suggest that pioglitazone may normalize cerebrovascular blood flow (CBF) in addition to reducing oxidative stress and inflammation [68, 69]. Improvement in cognition has been shown when pioglitazone is given to aMCI and AD subjects with comorbid DM II [70–72]. Cognitive improvement in treatment groups was also associated with increased A β (1–40/1–42) ratios, improved CBF, and reduced tumor necrosis factor- α levels [70, 72]. Conversely, cognitive improvement was not demonstrated in AD subjects that did not have comorbid DM II [73].

Glucagon-Like Peptide-1 Analogs

Three glucagon-like peptide-1 analogs have been studied in relation to AD. Liraglutide is used for the treatment of DM II, but affects insulin levels only when blood glucose levels are elevated. An in vitro study demonstrated neuroprotective effects and improved long-term potentiation with liraglutide treatment (table 4) [74]. A different study based on AD animal models also described reduced cerebral A β oligomers, neurogenesis in the dentate gyrus, and anti-inflammatory activity [75]. Exenatide has only been studied in vitro, in which it has demonstrated neuroprotective benefits and reversal of tau hyperphosphorylation (table 1) [76, 77]. Liraglutide and lixisenatide have been shown to cross the BBB in an animal model, with the latter inducing neurogenesis within the dentate gyrus (tables 2, 4) [78].

Insulin

Investigational treatments of AD using DM medication was in response to an increased incidence of AD in individuals with DM II. Researchers hypothesized that insulin resistance and insensitivity may be risk factors for AD. Both insulin and A β oligomers bind to neurons resulting in opposing effects. A β reduces insulin receptors whereas insulin reduces A β oligomer binding sites, though the opposing actions are not due to competitive inhibition [57].

Several animal studies and clinical trials using insulin have been conducted in the context of AD (table 4). Animal models have demonstrated changes to the pathology underlying AD including increased A β (1–40) oligomer clearance, decreased expression of A β (1–40), and neuroprotection from the toxic effects of A β [79, 80]. Clinical trials in aMCI and AD used an intranasal administration of the drug to ensure central nervous system penetration and to prevent the reduction of plasma glucose levels. Intranasal insulin increased plasma A β (1–42) levels in all subjects, regardless of APOE-4 allele status, but resulted in cognitive improvement in non-APOE-4 carriers in only one study [81, 82]. A later trial using an intranasal formulation of insulin found memory and functional improvements in subjects regardless of APOE-4 genotype [83]. Treatment effects correlated with the cerebrospinal fluid tau/A β (1–42) ratio and reduced progression of brain hypometabolism typically observed on brain fluorodeoxyglucose positron emission tomography scans in AD patients. Several of these studies have also described an inverted ‘U’-shaped dose response effect with low and high doses of intranasal insulin having minimal effects on study end points. Treatment response also appears to be related to insulin itself as opposed to other metabolic effects [84].

Statins

Statins inhibit hydroxymethylglutaryl coenzyme A reductase which leads to decreased cholesterol synthesis through their action in the liver. Hypercholesterolemia has been shown to be a risk factor for AD in human epidemiological studies, and animal models have shown that hypercholesterolemia increases cerebral A β deposition [85]. Cholesterol increases APP cleavage by β - and γ -secretase leading to formation of A β as shown by cellular and animal models. As statins decrease cholesterol levels, it has been theorized that they may decrease A β production, and preclinical studies have supported this (table 4). Both cellular and animal models have shown decreased A β production when statins are used [85]. Studies in humans have been less conclusive to date. Observational studies have shown a correlation between statin use and decreased risk of AD, and lovastatin has been associated with decreased serum A β in cognitively normal humans. However, multiple randomized controlled trials have failed to show an effect of statins on AD [86–88]. There are multiple theories for this discrepancy. The first involves the ability for statins to cross the BBB. Statins may be lipophilic (e.g. cerivastatin, lovastatin, simvastatin) or hydrophilic (i.e. atorvastatin, fluvastatin, pravastatin) and lipophilic statins cross the BBB more readily. Both lipophilic and hydrophilic statins have been studied in prior human trials. In addition, fluvastatin is negatively

charged and may be repelled by the BBB endothelial cells. Alternatively, it has been theorized that methodological and design problems have led to the negative studies including the timing and duration of statin use, dose, disease level, and accurate diagnosis of AD [88].

Antihypertensives

Hypertension is associated with an increased risk of vascular dementia and AD and several studies have examined potential treatment effects of several different classes of antihypertensive medications in AD. Of those, β -blockers and hydrochlorothiazide have been shown to decrease the risk of incident dementia in human population studies (table 3) [89, 90]. β -Blocker effects may be mediated via anti-inflammatory mechanisms or through improved cardiac output in subjects with subclinical congestive heart failure [89]. Unfortunately the study examining the preventive effects of hydrochlorothiazide was not designed to detect the direct antidementia MOA but rather to measure the effects of blood pressure reduction on the incidence of dementia [90].

Calcium Channel Blockers

Calcium channel blockers (CCBs) are antihypertensive medications that mediate the influx of cellular calcium and are divided into two groups: dihydropyridine and nondihydropyridine. Dihydropyridine CCBs have been the most studied of the two groups in AD.

Of the dihydropyridine CCBs, nilvadipine is only unique in that it has been researched the most in relation to AD (table 4). In vitro studies have demonstrated inhibition of cerebral artery vasoconstriction and $A\beta$ production [91, 92]. Animal studies have similarly shown restored regional CBF, increased clearance of $A\beta$, and subsequent improvements in learning and memory in nilvadipine-treated mice [91, 92]. Patients with aMCI who were treated chronically with nilvadipine failed to progress to dementia compared to control subjects [93] and patients diagnosed with AD also maintained clinical stability regardless of pretreatment blood pressure [94]. Treatment with nilvadipine was well tolerated [95]. A phase 3 trial of nilvadipine is currently being conducted in Europe.

Some but not all other dihydropyridines have similar effects to nilvadipine suggesting that the underlying mechanisms related to AD treatment are not inclusive to this class of CCBs. Nilvadipine and amlodipine inhibited $A\beta$ production in vitro, but other dihydropyridines had no effect or raised $A\beta$ production [92]. Amlodipine did not reduce cerebral $A\beta$ load in animal models nor did it decrease conversion from aMCI to AD in clinical trials (table 2) [92, 93]. Nitrendipine increased the clearance of $A\beta$ and improved regional CBF in animal models and also reduced the incidence of AD-related dementia in subjects with isolated systolic hypertension (table 4) [90, 92]. Nimodipine was the subject of a Cochrane Review in 2002 that concluded it had possible benefits in the treatment of AD, vascular dementia, and mixed dementia presumably due to its neuroprotective effects (table 4) [96, 97]. Like nimodipine, isradipine has neuroprotective effects downstream of $A\beta$ oligomer formation but isradipine may have more brain bioavailability compared to nimodipine (table 1) [97]. The two nondihydropyridine CCBs that have been studied in the context of AD are verapamil and diltiazem. Both ameliorate neurotoxicity caused by $A\beta$ and verapamil may also reduce $A\beta$ (1–40) oligomer levels (table 4) [45, 97, 98].

Angiotensin-Related Compounds

Two classes of antihypertensive medications antagonize the activity of angiotensin, angiotensin-converting inhibitors and angiotensin receptor blockers (ARBs). Both classes of medications are associated with a decreased incidence of all-cause dementia, though the association is strongest with ARBs (table 3) [99]. The angiotensin-converting inhibitor enalapril reduced the incidence of dementia, including AD, in subjects with isolated systolic

hypertension [90]. The mechanisms underlying these results are unclear as another angiotensin-converting inhibitor, captopril, did not affect cerebral levels of A β [100]. The mechanism underlying ARBs' anti-AD effects are also cryptic as studies have reported conflicting results on its effect on cerebral A β levels, though its effects may be mediated by decreased oligomerization of A β [100, 101]. Other ARBs have similarly not affected A β levels despite ameliorating cognitive and cerebrovascular dysfunction [100, 102].

Antiepileptic Drugs

Valproic acid, a drug used for bipolar disorder and epilepsy, has been proposed as a neuroprotective agent for AD. The proposed MOA is complex, but it may act by inhibiting proinflammatory cytokine production and by enhancing microglial phagocytosis of A β (table 4) [103, 104]. Animal models have demonstrated inhibition of glycogen synthase kinase-3 β -mediated γ -secretase cleavage of APP both in vitro and in vivo. Valproic acid treatment significantly reduced neuritic plaque formation and improved memory deficits in transgenic AD model mice [105]. A recent trial in AD showed no effect on the emergence of behavioral changes or on cognitive decline [106].

Antidepressants

Tricyclic Antidepressants

Amitriptyline, a tricyclic antidepressant, is used to treat depression, migraine, and neuropathic pain. Patients taking amitriptyline have an increased serum concentration of brain-derived neurotrophic growth factor, and AD animal models have shown that it increases hippocampal brain-derived neurotrophic growth factor and dentate gyrus neurogenesis (table 4) [107, 108]. Cellular models show that amitriptyline binds to the neurotrophin receptors, TrkA and TrkB, which may prevent apoptosis and promote neurite outgrowth [109]. Although it may increase total A β in animal models, this is due to an increase in the nontoxic A β monomer while decreasing the toxic A β dimer [110]. Alternatively, some non-AD animal models have suggested that amitriptyline may have a proapoptotic effect [110]. Nortriptyline may stop the formation of mitochondrial permeability transition pores and release of cytochrome c preventing apoptosis (table 2) [110].

Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors are a frequently used class of antidepressant and may have an effect on AD. In an AD mouse model, multiple selective serotonin reuptake inhibitors, including fluoxetine, citalopram and desvenlafaxine (a serotonin and norepinephrine reuptake inhibitor), decreased A β levels, and chronic treatment with citalopram reduced the amount of amyloid plaque (tables 2, 4). Activation of extracellular regulated kinase by serotonin was necessary for this effect [111]. Correlating with this, a brain positron emission tomography study of normal humans using Pittsburgh compound B showed decreased A β plaque burden in participants who had been taking selective serotonin reuptake inhibitors [111]. Fluoxetine and sertraline have been shown to increase brain-derived neurotrophic growth factor leading to hippocampal neurogenesis while fluoxetine additionally decreases oxidative phosphorylation [110, 112–114]. Paroxetine increases brain-derived neurotrophic factor and has also been shown to reduce levels of A β and p-tau while preserving cognitive function in AD mouse models [110, 115, 116].

Monoamine Oxidase Inhibitors

Deprenyl (selegiline) and rasagiline are selective monoamine oxidase-B inhibitors commonly used in Parkinson's disease. They both have shown neuroprotective properties in cellular and animal models. They protect against apoptosis by stopping the decrease in

mitochondrial membrane potential, preventing the activation of caspase-3 and poly-ADP ribose polymerase-1, and increasing Bcl-2 and Bcl-xl while decreasing Bad and Bax. In addition, they have been shown to stimulate the cleavage of APP by α -secretase in animal models (table 4) [117–119]. The advantage of rasagiline is it does not have the toxic amphetamine metabolites of deprenyl [118].

Ladostigil is a new multifunctional drug which combines the neuroprotective effects of monoamine oxidase-A/B inhibition with the cognitive enhancement of cholinesterase inhibition. Animal models have shown it protects against apoptosis and induces cleavage of APP by α -secretase possibly through activation of mitogen-activated protein kinase and protein kinase C (table 4). It inhibits acetyl- and butyrylcholinesterase leading to improved cognition [118–120].

Lithium

Lithium is a mood stabilizer most often used in bipolar disorder. It is an inhibitor of glycogen synthase kinase-3 β . This is a transcription regulator and, when inhibited by lithium in both cellular and AD mouse models, will lead to decreased A β production and tau phosphorylation. Lithium may also inhibit mitochondrial membrane depolarization and cytochrome-c release which prevents apoptosis and promotes neuronal survival by increasing Bcl-2 (table 4) [110, 121]. Clinical trial results have shown mixed results. A single-blind trial of lithium in AD showed no benefit on cognitive or biomarker outcomes [122], whereas a trial in aMCI demonstrated reduced levels of p-tau in the CSF and improved performance compared to placebo on several measures of cognition [123].

Antipsychotics

The atypical antipsychotics are commonly used in AD and other dementias for the treatment of psychosis and behavioral symptoms. Some animal models have shown that they may have an effect on the disease pathology as well. Risperidone may protect against A β -induced apoptosis but at the same time may inhibit mitochondrial-complex-1 (table 2) [110]. Quetiapine protects against A β -induced reactive oxygen species and caspase-3 activation, preventing apoptosis, and it may also inhibit complex-1 (table 2) [110]. Olanzapine protected against apoptosis and increased neurogenesis in the dentate gyrus in a rat model (table 2) [110, 124]. It has been hypothesized in the past that olanzapine may benefit cognition through antagonism of cholinergic neuron receptors M2, 5HT3, and 5HT6. Multiple short-term clinical trials in AD have shown a worsening of cognition when treated with atypical antipsychotics [125, 126].

Antiasthma Compounds

A recent study has investigated the use of the antiasthmatic drug zileuton for the treatment of AD (table 2) [127]. Zileuton was postulated to have anti-AD effects through its blockage of 5-lipoxygenase, which is higher in AD patients. Genetic knockout mice for this enzyme reduced A β levels in mice. Similarly, zileuton's inhibition of 5-lipoxygenase resulted in reduced cerebral A β deposition in transgenic mice that were treated with the compound. Further analyses demonstrated significant reductions in γ -secretase complex levels without affecting Notch signaling.

Anti-Inflammatory Medications

Ibuprofen and other nonsteroidal anti-inflammatory drugs such as naproxen, have several anti-inflammatory effects that have been hypothesized as a potential MOA for neuroprotection in AD. Human epidemiological studies from the last decade have suggested protective effects of nonsteroidal anti-inflammatory drugs (table 4) [128]. Cyclooxygenase-1

suppression is believed to protect neurons against immune-mediated damage in the early stages of AD pathogenesis [129] and cyclooxygenase-mediated oxidation facilitates calcium-dependent glutamate signaling pathways involving N-methyl-D-aspartate, directly protecting neurons by reduction of cellular responses to glutamate [128]. Nonsteroidal anti-inflammatory drugs, such as ibuprofen, have been of interest for additional properties that may be important for treating AD. These drugs also affect γ -secretase activity without significantly disrupting other APP processing pathways or Notch cleavage [130]. γ -Secretase modulators are proposed to act as modulators of γ -cleavage of APP away from production of toxic A β (1–42) [129]. The anti-inflammatory medication used commonly in gout, colchicine, has antiamyloidogenic effects first studied in the prevention and treatment of amyloidosis complicating familial Mediterranean fever [131] and is thought to inhibit internalization of membrane-bound APP and suppress mononuclear cell activity and cytokine release (table 4). Colchicine has also been proposed to have effects on the production of amyloidogenic fragments, by acting through lysomotropic properties to inhibit internalization of membrane-bound APP [132]. Hydroxychloroquine is believed to inhibit inflammatory cytokine release from stimulated monocytes (table 1) [133].

The purified immunoglobulin and anti-inflammatory therapy, intravenous immunoglobulin, has been studied in AD as it contains human antibodies against A β [134] and is proposed to protect neurons by enhancing microglia-mediated clearance of natively formed diffuse human A β deposits in the brain (table 4) [135]. Intravenous immunoglobulin was found in a retrospective analysis to reduce the risk of developing AD [136], and further small-scale prospective clinical trials have suggested beneficial effects [137]. Phase 3 trials examining the effects of intravenous immunoglobulin in AD are in progress.

Antiparkinsonian Medications

Apomorphine, a dopamine receptor agonist, used in Parkinson's disease, has been studied at the cellular level as an inhibitor of A β fibril formation (table 4) [138]. Animal studies have demonstrated action through extracellular A β -degrading proteases, and stimulation of catabolism of intracellular A β via activation of the ubiquitin-proteasome pathway [139]. Furthermore, apomorphine also exhibits antioxidant effects [139]. Pramipexole, a dopamine agonist used in Parkinson's disease, has been proposed as an agent to protect cells against formation of oligomers and fibrils of A β , which is hypothesized to prevent cell death and reduce the amount of free radicals in neurons (table 1) [140].

Methylene Blue

Methylene blue (MB) is a compound that is used to treat toxicities such as carbon monoxide poisoning. MB delays mitochondrial dysfunction induced by hydrogen peroxide and cadmium by increasing mitochondrial complex IV, which is typically decreased in AD (table 4) [141]. Low doses of MB administered to transgenic rats increased cytochrome-c oxidase activity and improved spatial memory [142]. MB also reduces tau levels by facilitating its degradation and clearance [143–146]. Neuroprotective effects of MB were observed with concomitant reduction of soluble tau levels in one study [147] and were not observed at all in another [148]. MB also affects the amyloid cascade; affecting A β oligomerization by promoting fibrillization [149] and facilitating degradation by increasing proteasome activity [150]. A clinical trial of MB in AD did not meet its primary outcome measure but may have shown clinical and biomarker benefit in patients followed after the trial [151].

Nicotine

In trials of AD, nicotine has shown symptomatic benefits, and several studies have also demonstrated possible disease-modifying effects. Early reports that cerebral A β levels were

decreased in AD patients who smoked as well as in nicotine-treated APP transgenic mice prompted researchers to investigate additional MOAs of nicotine (table 4) [152]. Nicotine exhibits neuroprotective effects in addition to lowering hippocampal A β (1–40) levels by preventing impairments in cognition, basal synaptic transmission, and long-term potentiation [153]. Other studies have been contradictory in that changes in A β levels and cognition were not observed or worsened cognition and enhanced tau phosphorylation were demonstrated [154, 155]. These differences are at least partially explained by the different animal models used in each study. In a recent trial of nicotine in aMCI, improvements were noted in attention, memory, and psychomotor speed in the treatment group, though the clinical global impression of change did not demonstrate any statistically significant difference [156]. Treatment was well tolerated and no withdrawal symptoms were noted. Future studies will likely examine AD-related biomarkers with nicotine treatment.

Trehalose

Trehalose, a glucose disaccharide, has been studied in cellular and tissue models demonstrating promotion of α -helical conformation of the A β peptide, which is thought to be more favorable than the normal coil configuration in membranes (table 1) [157].

Dantrolene

Dantrolene, a ryanodine receptor inhibitor, acting on calcium channels has been hypothesized to affect AD through actions on presenilins, in that presenilins function as endoplasmic reticulum calcium leak channels in neurons at ryanodine receptors and inositol triphosphate receptors (table 4) [158, 159]. There is evidence that suggests neuronal calcium signaling disruptions may play a role in AD pathogenesis [160].

Discussion

A number of approved agents with effects relevant to AD have been described (tables 1–4) and could provide the starting points for repurposed drug development programs. A variety of types of studies and sources of information provide insight into these agents – observations in transgenic animals and other AD models, epidemiological observations, and combinations of data have all contributed to this data set. The observations suggest agents that might be considered in drug development programs or pathways and preliminary molecular structures that might be exploited for the treatment of AD.

As a drug discovery strategy, repurposing has the advantage of identifying molecules that meet traditional criteria for druggability since they have already been optimized for these features. Repurposing is less likely to identify compounds with unusual characteristics such as those required for inhibition of protein-protein interaction [161]. Repurposed agents may not be ideal for the new indication and require thorough pharmaceutical medicine review. The drug has been optimized for the original indication and the same molecule may not be optimal for the new indication. Such an agent can serve as a founder molecule for a new drug discovery program. Similarly, doses may differ for different indications and a dose-finding trial may be required.

Regulatory standards for toxicity evolve steadily and the original toxicity studies may no longer suffice for submission for the new indication.

Intellectual property issues can be particularly challenging for repurposed compounds. Patent life may be limited at the time the new indication is discovered. Dose, formulation, or method of use patents may provide avenues of attaining sufficient intellectual property rights to support advancing the compound through development [162]. Geographic approaches may

allow market exclusivity in some countries. Even compounds with limited patent protection and intellectual property may provide a scaffold for new drug discoveries leading to compounds with better intellectual property positioning. Abandoned compounds that never advanced to final development may have substantial residual intellectual property protection.

Extrapolation from animal models such as transgenic mouse models to human AD is challenging. Transgenic models are typically created with APP or APP and presenilin (PSEN1 or 2) mutations to create animals that overproduce A β protein. These mice do not exhibit neurofibrillary tangles or cell death and recapitulate only part of the AD pathology. Activity in a transgenic mouse may establish anti-A β activity but does not necessarily provide evidence of effectiveness in human AD. Testing in more than one model and using models that explicate specific MOA effects may provide more confidence for advancing a compound to human development [163].

Broadened use of electronic medical records (EMR) in combination with bioinformatics can also help with drug repurposing and development. Because of the high prevalence of AD, medication-related prevention, delay, or slowed progression of AD may be ascertainable at the population level. Large EMR databases with diagnosis and medication data can be de-identified and analyzed for such associations. Although, more easily accomplished in countries with national healthcare systems, this process can also be employed within the US large healthcare systems with established EMRs (e.g. Veterans Healthcare Service and Cleveland Clinic Foundation). The growth of bioinformatics and distributed computing will assist in this undertaking. Using EMRs is an example of how research may be aided and accelerated by moving away from hypothesis-driven research towards data-derived models [164]. Using past experiences, including basic science and epidemiological research, increases efficiency and effectiveness of medical record research strategies. The analysis of large databases of existing drug and disease data such as EMRs and published biomedical literature [165, 166] can assist research strategy and identify agents for repurposing in AD.

One drawback to repurposing drugs is that they are already available to physicians and consumers. Such wide availability of drugs with known toxicities may prompt clinical off-label use. Such practices raise safety concerns as well as the ability to conduct unbiased clinical trials. ‘Drop-ins’ may occur in placebo groups if patients decide to take available medications on their own while in a trial. These behaviors may all affect trial outcomes.

There is an urgent need to find new treatments for AD as the number of cases continues to rise and the impact on families and society increases. Methods of abbreviating the time of drug development can help accelerate developing new therapies and getting them to patients faster. Drug repurposing is one channel for more rapid translation of pharmacological information into important new therapies.

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