Alzheimer's & Dementia: Translational Research & Clinical Interventions 2 (2016) 222-232

Featured Article

Alzheimer's drug-development pipeline: 2016

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Abstract

Background: Alzheimer's disease (AD) is growing in frequency and new therapies are urgently needed.
Methods: We assessed clinicaltrials.gov (accessed 1-4-2016) to determine the number and characteristics of trials in phase I, phase II, and phase III for treatment of AD.
Results: There are currently 24 agents in 36 trials in phase III of AD drug development. Seven of these 24 agents are symptomatic cognitive-enhancing compounds, and 17 are disease-modifying treatments (DMTs). Most DMTs address amyloid-related targets (76%). There are 45 agents in phase II being assessed in 52 clinical trials. Phase II trials include 30 DMTs, with 26 small molecules and 4 immunotherapies. There are 24 agents in the first phase of AD drug development.
Discussion: Amyloid is the principal target of late-stage development programs. There are relatively few agents in clinical trials for AD suggesting a need to amplify the drug discovery ecosystem.

Keywords: Alzheimer's disease; Drug development; Phase I; Phase II; Phase III; Biomarkers; Amyloid; Tau; Cognitive enhancement

Alzheimer's disease (AD) is rapidly becoming a major public health threat with increasing numbers of affected individuals as the world's population ages. There are currently 5.3 million Americans and 35 million people worldwide with AD dementia, and the number will increase to nearly 15 million in the United States and over 100 million globally by 2050 if treatments are not found [1,2].

New therapies are needed for this burgeoning population of affected and at-risk persons that improve the symptoms of patients with memory and cognitive decline, prevent or delay the onset of AD in individuals who are at-risk for the disease, or slow progression in those with declining cognition. New therapies are being assessed in clinical trials but the success rate of AD drug development has been low with the last new novel agent approved in 2003 [3].

To gain insight into the current AD treatment pipeline, we reviewed all trials registered in clinicaltrials.gov (accessed 1/4/2016), the US government website that lists all US and most global clinical trials. Registration of new trials on the site is required for trials approved by the US Food and Drug Administration (FDA) since 2007 [4]. We reviewed this comprehensive website for all agents in clinical trials for AD dividing them into those in phase I, phase II, and phase III. The purpose of the study was to understand the landscape of AD drug development and determine

Dr. Cummings has received research support from Avid Pharmaceuticals, Teva Pharmaceuticals, and CogState. Dr. Cummings has provided consultation to Abbvie, Acadia, Actinogen, ADAMAS, Alkahest, Alzheon, Anavex, Astellas, Astra Zeneca, Avanir, Axovant, Biogen Idec, Biotie, Boehinger-Ingelheim, Chase, Eisai, Forum, GE Healthcare, Genentech, Grifols, Intracellular Therapies, IRIS, Ionis Pharmaceuticals, Lilly, Lundbeck, MedAvante, Merck, Neurotrope, Novartis, Nutricia, Otsuka, Pfizer, Predemtec, Probiodrug, QR Pharma, Resverlogix, Roche, Servier, Sunovion, Suven, Takeda, Toyoma, Transition Therapeutics, and United Neuroscience, companies. Dr Cummings owns the copyright of the Neuropsychiatric Inventory. Dr Cummings has stock options in Prana, Neurokos, ADAMAS, MedAvante, and QR pharma. Mr. Morstorf and Ms. Lee have no conflicts of interest.

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http://dx.doi.org/10.1016/j.trci.2016.07.001

evolutions occurring in AD drug development from historical practices. The goal is to assess the state of AD drug development, anticipate the emergence of new therapies, review emerging pharmacologic mechanisms and clinical trial approaches, and derive lessons possibly helpful in the drug development process.

1. Methods

We interrogated clinicaltrials.gov with the information summarized here accessed on January 4, 2016. We used the search features of the site to capture all agents listed for AD in phase I, II, and III. We captured the trial title, beginning date, anticipated ending date, anticipated duration, number of subjects to be enrolled, number of arms of the study (usually a placebo arm and one or more treatment arms with different doses of the test agent), whether a biomarker was described, and whether the sponsor was a biopharma company, the National Institutes of Health (NIH), a combination of biopharma and NIH, or "other." We included trials that were recruiting, active but not recruiting—trials that have completed recruiting and are continuing as the efficacy or safety of the agent is being determined—and enrolling by invitation. We did not include trials listed as not yet recruiting, completed, terminated, suspended, or withdrawn. These exclusions were based on our interest in the currently active pipeline and what agents could evolve in the near term. Reasons for terminating, suspending, or withdrawing trials are often not provided, and we could not draw conclusions about these trials or the agents involved. The agents and trials reviewed comprise a comprehensive list of agents currently in trials. The list is not exhaustive because not all non-US trials are registered on clinicaltrials.gov, and there is sometimes a delay in registering trials. The mechanism of action of each agent was determined from the information on clinicaltrials.gov (e.g., the mechanism is often noted in the title of the trial or in a description of the trial) or from a comprehensive search of the literature if the mechanism was not provided on the federal website. In a few cases, the mechanism is undisclosed. We grouped the mechanisms into symptomatic or disease modifying. We further divided the symptomatic agents into those that were putative cognitive-enhancing agents or those that addressed neuropsychiatric symptoms. Disease-modifying therapies (DMT) were divided into those that targeted amyloid-related targets, those that aimed at modifying tau-related mechanisms and those with "other" mechanisms such as neuroprotection or metabolic effects [5]. The definitions of disease-modification and neuroprotection are controversial and evolving [6,7]; the terminology is used here to conveniently classify the types of mechanisms for agents in current AD drug-development programs. We did not include nonpharmacologic therapeutic approaches such as devices, cognitive therapies, and medical foods.

2. Results

There are currently 93 agents in some phase of drug development for AD. Fig. 1 provides a comprehensive overview of the agents currently in clinical trials for AD.

2.1. Phase III

There are 24 agents in 36 trials in phase III of AD drug development. Eight agents are in two or more clinical trials. Of the agents in trials, seven are symptomatic treatments targeting neurotransmitter pathways with cognitive enhancement (3) or neuropsychiatric (4) effects. Encenicline, a nicotinic cognitive-enhancing agent, was put on clinical hold by the FDA pending the review of gastrointestinal effects seen in some trial participants. Of the 17 DMTs in phase III, 12 are small molecules, and 5 are immunotherapies. All the immunotherapies and 8 of the 12 small molecules are directed at amyloid-related targets. There are four beta-site amyloid precursor protein cleaving enzyme (BACE) inhibitors in phase III trials. Amyloid-targeting agents comprise 76% of the late-stage DMT pipeline. There is one antitau agent in phase III—TRx0237.

The mean duration of trials of symptomatic agents was 23.3 weeks; the mean duration of DMT trials was 114.1 weeks. In these phase III trials, the mean number of subjects per arm for symptomatic trials is 392.2 and for trials of DMT agents is 516.1.

Eighty-eight percent (32 of 36) of trials are sponsored by the biopharma industry, 2 are jointly sponsored by NIH and industry, and 2 are sponsored by "other" entities.

Table 1 shows the agents in phase III with their mechanism of action.

2.2. Phase II

There are 45 agents in phase II of AD drug development being assessed in 52 clinical trials. The pipeline includes 12 symptomatic cognitive-enhancing agents and three agents addressing neuropsychiatric symptoms. There are 30 DMTs being studied in phase II drug development programs; 26 of these are small molecules and four are immunotherapies. Amyloid-related targets comprise the mechanism of action of nine of the 26 small molecules and all four of the immunotherapies. Forty-three percent of phase II DMTs have amyloid-targeting mechanisms of action. Sixteen agents have "other mechanisms" including ten putative neuroprotective agents and six addressing metabolic problems. There is one antitau agent in phase II and one stem cell program (with two trials) in phase II of development.

Phase II trials of symptomatic agents have a mean duration of 19.1 weeks and trials of DMTs in phase II have a mean duration of 49.5 weeks. On average, there are 67.1 subjects per arm in phase II trials of symptomatic treatments and 76.9 subjects per arm in trials of DMT agents.

Of the 52 trials for the 45 agents, 29 are industry-sponsored, four are sponsored by NIH, and 18 are sponsored

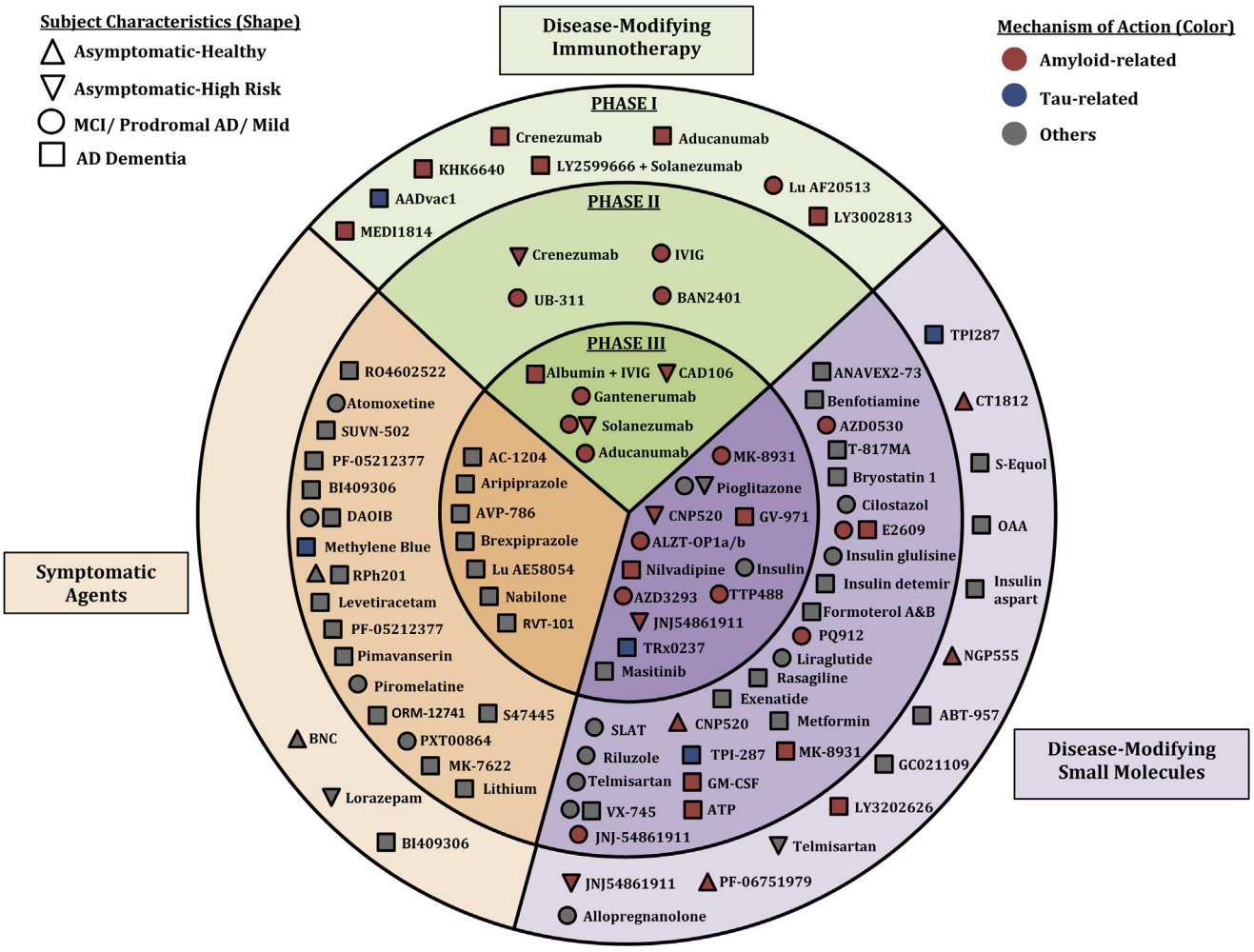

Fig. 1. Agents currently in clinical trials for AD (shape indicates stage of disease of patients in the trials; color shows the mechanism of action; location shows phase of development and category of activity—immunotherapy, disease-modifying small molecule, symptom-reducing small molecule).

by "other" entities such as academic medical centers and philanthropic foundations. One trial is jointly sponsored by NIH and industry.

Table 2 shows the agents in phase II with their mechanism of action.

2.3. Phase I

There are 24 agents in phase I AD drug-development programs. Of these, three are symptomatic agents, 13 are small molecule DMTs, and eight are DMT immunotherapies. Five of the 13 small molecules and seven of the eight immunotherapies address amyloid-related mechanisms (57% of the DMT mechanisms). One tau-directed antibody and one tau-related small molecule are included in the AD phase I pipeline. Five neuroprotective agents and two metabolic agents are being assessed.

Of the 27 trials of phase I agents, 20 are sponsored by the biopharma industry, two are funded by NIH, one is jointly supported by NIH and industry, and four are funded through other mechanisms.

Table 3 shows the agents in phase I with their mechanism of action.

2.4. Biomarkers

Biomarkers are playing an increasingly important role in clinical trials of DMTs. Not all trials on clinicaltrials.gov state if biomarkers are included in their trials or discuss the type of biomarkers included, and we discuss the percent of trials that describe which biomarkers are included (Table 4). In current phase III trials, measurement of cerebrospinal fluid (CSF) amyloid beta protein (Aβ) is the most commonly used biomarker (27.7% of trials reporting use of biomarkers), followed by volumetric magnetic resonance imaging (MRI; 25%), CSF tau, and amyloid positron emission tomography (PET; 22.2% each), fluorodeoxyglucose (FDG) PET (19.4%), plasma amyloid (8.3%), and tau PET (2.7%). Phase II biomarkers include CSF amyloid (25%), CSF tau (21.2%), volumetric MRI (15.4%), FDG PET (11.5%), amyloid PET (9.6%), plasma amyloid (5.8%), and plasma tau (3.8%).

Table 1
Agents currently in phase III of development and their mechanism of action (as of 1/4/2016)

Agent	Agent mechanism class	Mechanism of action	Clinicaltrials.gov ID	Sponsor	Start date	Estimated end date
AC-1204	Metabolic	Ketogenic agent	NCT01741194	Accera	Mar 13	Oct 17
Aducanumab	Antiamyloid	Monoclonal antibody	NCT02484547	Biogen	Sep 15	Feb 22
			NCT02477800	Biogen	Aug 15	Feb 22
Albumin + Immunoglobulin	Antiamyloid	Polyclonal antibody	NCT01561053	Instituto Grifols, S.A.	Mar 12	Dec 16
ALZT-OP1a + ALZT-OP1b	Antiamyloid	Antiamyloid combination (undisclosed target)	NCT02547818	AZTherapies	Sep 15	Mar 18
Aripiprazole	Neurotransmitter based	Atypical anti-psychotic	NCT02168920	Otsuka	Jun 14	Jul 17
AVP-786	Neurotransmitter based	Mixed transmitter effect	NCT02442765	Avanir	Sep 15	Jul 18
			NCT02446132	Avanir	Dec 15	Jul 19
AZD3293	Antiamyloid	BACE inhibitor	NCT02245737	AstraZeneca	Sep 14	May 19
Brexpiprazole (OPC-34712)	Neurotransmitter based	Atypical anti-psychotic	NCT01862640	Otsuka	Jul 13	Jun 17
			NCT01922258	Otsuka	Sep 13	Jun 17
CAD106	Anti-amyloid	Amyloid vaccine	NCT02565511	Novartis	Nov 15	Aug 23
CNP520	Anti-amyloid	BACE inhibitor	NCT02565511	Novartis	Nov 15	Aug 23
Gantenerumab	Anti-amyloid	Monoclonal antibody	NCT02051608	Hoffmann-La Roche	Mar 14	Mar 19
			NCT01224106	Hoffmann-La Roche	Nov 10	Oct 20
			NCT01760005*	Washington University School of Medicine	Dec 12	Dec 19
Idalopirdine (Lu AE58054)	Neurotransmitter based	5-HT6 antagonist	NCT02079246	H. Lundbeck A/S	Apr 14	Oct 17
			NCT02006654	H. Lundbeck A/S	Mar 14	Mar 17
			NCT02006641	H. Lundbeck A/S	Feb 14	Mar 17
			NCT01955161	H. Lundbeck A/S	Oct 13	Oct 16
Insulin (Humulin)	Metabolic	Metabolic agent	NCT01767909	University of Southern California	Sep 13	Feb 17
JNJ-54861911	Anti-amyloid	BACE inhibitor	NCT02569398	Janssen	Oct 15	May 23
Masitinib	Anti-inflammatory, neuroprotective	Tyrosine kinase inhibitor	NCT01872598	AB Science	Jan 12	Dec 16
MK-8931 (Verubecestat)	Anti-amyloid	BACE inhibitor	NCT01953601	Merck Sharp & Dohme Corp.	Nov 13	Mar 21
Nabilone	Neurotransmitter based	Cannabinoid (receptor agent)	NCT02351882	Sunnybrook Health Sciences Centre	Jan 15	Dec 17
Nilvadipine	Anti-amyloid	Calcium channel blocker	NCT02017340	St. James's Hospital, Ireland	Oct 12	Dec 17
Pioglitazone	Metabolic	PPAR-gamma agonist; anti-amyloid effect	NCT02284906	Takeda	Feb 15	Apr 21
			NCT01931566	Takeda	Aug 13	Jul 19
RVT-101	Neurotransmitter based	5-HT6 antagonist	NCT02585934	Axovant Sciences	Oct 15	Oct 17
Sodium oligo-mannurarate (GV-971)	Anti-amyloid	Anti-amyloid agent	NCT02293915	Shanghai Greenvalley Pharmaceutical Co., Ltd.	Apr 14	May 17
Solanezumab	Anti-amyloid	Monoclonal antibody	NCT02008357	Eli Lilly and Company	Feb 14	Apr 20
			NCT01127633	Eli Lilly and Company	Dec 10	Nov 18
			NCT01900665	Eli Lilly and Company	Jul 13	Oct 18
			NCT01760005*	Washington University School of Medicine	Dec 12	Dec 19

TRx0237	Antitau	Anti-tau agent	NCT02245568	TauRx Therapeutics	Aug 14	Jan 17
			NCT01689246	TauRx Therapeutics	Jan 13	Nov 15
			NCT01689233	TauRx Therapeutics	Oct 12	May 16
TTP488 (Azeliragon)	Anti-amyloid, anti-inflammatory	Anti-amyloid RAGE antagonist	NCT02080364	TransTech Pharma	Apr 15	Mar 18

Abbreviations: BACE, beta-site amyloid precursor protein cleaving enzyme; PPAR, peroxisome proliferator-activated receptor; RAGE, receptor for advanced glycation end products.
NOTE. Twenty-four agents in 36 phase III clinical trials currently ongoing (active, not recruiting, and active, recruiting) as of January 4, 2016 according to clinicaltrials.gov.
*Same trial studying gantenerumab and solanezumab independently.

3. Discussion

This analysis of clinicaltrials.gov reveals that there are relatively few agents in AD drug-development programs. The high failure rate in AD drug development and the small number of drugs being assessed suggest that the emergence of a repertoire of AD agents that could be tailored to fit the individual needs of patients is unlikely. The small number of agents in phase I is especially concerning as this phase is the major source of drugs for later stage development. A few repurposed agents can enter at phase II or phase III, but these agents generally have limited patent lives or limited intellectual property opportunities and do not comprise a major source of new candidate compounds [8]. Likewise, immunotherapies often begin in phase I/phase II with patients diagnosed with AD to avoid the risk of permanently altering the immune system of normal volunteers but, as can be seen, there are only a few such agents entering the drug-development pipeline. Overall, the AD ecosystem of AD drug development must be altered to yield more targets and more candidate therapies if a robust pipeline of therapies is to be established.

Other reviews of AD drug development have led to similar conclusions as those presented here. The comprehensive 2010 review by Mangialasche et al. [9] showed that new approaches to cholinergic therapy and many antiamyloid trials were being pursued. There were more agents directed toward tau-related targets in the 2010 pipeline review; most of these have since failed. Fig. 1 is similar to the visualization approach used by Mangialasche et al. [9] and can be used to compare changes over a 6-year period. Similarly, Cummings et al [3] found—using a similar strategy to that used in the current review—that there were relatively few drugs being assessed and that the overall failure rate for AD drug development was a dramatic 99.6%. They also noted that no new novel drugs for AD had been approved since 2003.

We compared AD drug development with oncology drug development to provide a perspective on the observed numbers. In the 2014–2015 period, 135 trials were registered for AD, whereas 4976 trials were registered for cancer (these figures were generated from clinicaltrials.gov using the same search terms as used in the reviewed AD trials and agents). This indicates that the number of agents in trials is much larger for cancer than for AD and the likelihood of finding effective therapies is greater. This disparity likely reflects several influences including the greater success of rate of cancer drug development (19.8% of development programs succeed in cancer vs less than 1 percent of AD drugs [3,10]). Thirty-one percent of FDA new drug approvals for 2015 were for oncology agents [11]. The low success rate of AD drug development discourages pharmaceutical companies from pursuing research in this area and reduces the enthusiasm of venture capitalists for investing in biotechnology companies whose products address AD-related targets. As a result, fewer targets are identified, and fewer candidate agents discovered and developed. The biological understanding of

Table 2
Agents currently in phase II of AD drug development and their mechanism of action (as of 1/4/2016)

Agent	Agent mechanism class	Mechanism of action	Clinicaltrials.gov ID	Sponsor	Start date	Estimated end date
Adenosine triphosphate	Antiamyloid	Inhibits amyloid misfolding and toxicity	NCT02279511	Fundació Clínic per la Recerca Biomèdica	Nov 14	Nov 16
ANAVEX 2-73	Neuroprotective	Sigma-1 receptor agonist	NCT02244541	Anavex Life Sciences Corp.	Dec 14	Oct 16
Atomoxetine	Antiamyloid	Adrenergic uptake inhibitor	NCT01522404	Emory University	Mar 12	Dec 17
AZD0530 (saracatinib)	Antiamyloid	Kinase inhibitor	NCT02167256	Yale University	Dec 14	Dec 16
BAN2401	Antiamyloid	Monoclonal antibody	NCT01767311	Eisai	Dec 12	Jul 18
Benfotiamine	Metabolic	Antioxidant	NCT02292238	Burke Medical Research Institute	Nov 14	Nov 19
BI 409306	Neuroprotective	PDE9 inhibitor	NCT02240693	Boehringer Ingelheim	Jan 15	Jun 17
			NCT02337907	Boehringer Ingelheim	Jan 15	May 17
Byrostatin 1	Neuroprotective	Protein kinase C inhibitor	NCT02431468	Neurotrope Bioscience	Jul 15	Apr 17
Cilostazol	Neuroprotective	PDE3 antagonist	NCT02491268	National Cerebral and Cardiovascular Center	Jul 15	Jul 18
CNP520	Antiamyloid	BACE inhibitor	NCT02576639	Novartis	Aug 15	Mar 16
CPC-201	Neurotransmitter based	Cholinesterase inhibitor + peripheral cholinergic antagonist	NCT02185053	Chase Pharmaceuticals Corporation	Jul 14	Mar 16
			NCT02434666	Chase Pharmaceuticals Corporation	Jan 15	Jul 16
Crenezumab	Anti-amyloid	Monoclonal antibody	NCT01998841	Genentech	Dec 13	Sep 20
DAOIB	Neurotransmitter based	NMDA enhancer	NCT02103673	Chang Gung Memorial Hospital	Feb 14	Sep 16
			NCT02239003	Chang Gung Memorial Hospital	Jan 12	Jul 16
E2609	Anti-amyloid	BACE inhibitor	NCT02322021	Eisai	Nov 14	Jul 19
Exenatide	Metabolic	Glucagon-like peptide 1 receptor agonist	NCT01255163	National Institute on Aging (NIA)	Nov 10	Dec 18
Formoterol A&B	Neuroprotective	Beta-2 adrenergic receptor agonist	NCT02500784	Palo Alto Veterans Institute for Research	Jan 15	Jul 16
hUCB-MSCs	Neuroprotective	Stem cell therapy	NCT02054208	Medipost Co	Feb 14	Feb 18
			NCT01547689	Affiliated Hospital to Academy of Military Medical Sciences, Beijing, China	Mar 12	Dec 16
Insulin detemir	Metabolic	Insulin	NCT01595646	University of Washington	Nov 11	Sep 15
Insulin glulisine	Metabolic	Insulin	NCT02503501	HealthPartners Institute for Education and Research	Aug 15	Sep 17
JNJ-54861911	Anti-amyloid	BACE inhibitor	NCT02406027	Janssen	Jul 15	Jun 24
			NCT02260674	Janssen	Nov 14	Jun 16
Levetiracetam	Neurotransmitter based	Anticonvulsant	NCT02002819	University of California, San Francisco	Jun 14	Jun 17
Liraglutide	Metabolic	Glucagon-like peptide 1 receptor agonist	NCT01843075	Imperial College London	Jan 14	Jan 17
Lithium	Neurotransmitter based	Ion channel modulator	NCT02129348	New York State Psychiatric Institute	Jun 14	Apr 19
Metformin	Metabolic	Insulin sensitizer	NCT01965756	University of Pennsylvania	Jan 13	Dec 16
Methylene Blue	Anti-tau	Tau inhibitor; neuronal stimulant	NCT02380573	University of Texas Health Science Center at San Antonio	Jul 15	Jul 18
MK-7622	Neurotransmitter based	Muscarinic agonist	NCT01852110	Merck	Oct 13	Apr 20
MK-8931	Anti-amyloid	BACE inhibitor	NCT01739348	Merck	Nov 12	Jul 19
NewGam 10% IVIG	Anti-amyloid	Polyclonal antibody	NCT01300728	Sutter Health	Jan 11	Nov 17

ORM-12741	Neurotransmitter based	Alpha-2c adrenergic receptor antagonist	NCT02471196	Orion Corporation	Jun 15	Feb 17
PF-05212377 (SAM 760)	Neurotransmitter based	5-HT6 receptor antagonist	NCT01712074	Pfizer	Nov 12	Dec 15
Pimavanserin tartrate	Neurotransmitter based	5-HT2A inverse agonist	NCT02035553	Acadia	Nov 13	Jun 16
Piromelatine	Neurotransmitter based	Melatonin receptor agonist; 5-HT 1A and 1D receptor agonist	NCT02615002	Neurim Pharmaceuticals	Nov 15	Dec 17
PQ912	Anti-amyloid, anti-inflammatory	Glutaminyl-peptide cyclotransferase inhibitor	NCT02389413	Probiodrug AG	Mar 15	Oct 16
PXT00864	Neurotransmitter based	Combination of acamprosate and baclofen	NCT02361242	Pharnext, SAS	Jun 13	Dec 15
Rasagiline	Neuroprotective	Monoamine oxidase B inhibitor	NCT02359552	The Cleveland Clinic	Feb 15	Dec 16
Riluzole	Neuroprotective	Glutamate receptor antagonist; glutamate release inhibitor	NCT01703117	Rockefeller University	Apr 13	Nov 17
RPh201	Neuroprotective	G-protein coupled receptor antagonist	NCT01513967	Regenera Pharma	Jan 12	Dec 16
S47445 (formerly CX1632)	Neurotransmitter based	AMPA receptor agonist; nerve growth factor stimulant	NCT02626572	Institut de Recherches Internationales Servier	Feb 15	Sep 17
Sagramostim (GM-CSF)	Anti-amyloid	Granulocyte colony stimulator; amyloid removal	NCT01409915	University of Colorado, Denver	Mar 11	Jul 16
Sembragiline (RO4602522)	Neurotransmitter based	Monoamine oxidase B inhibitor	NCT01677754	Hoffmann-La Roche	Nov 12	Jun 15
Simvastatin + L-Arginine + Tetrahydrobiopterin	Neuroprotective	HMG-CoA reductase inhibitor and antioxidant	NCT01439555	University of Massachusetts, Worcester	Nov 11	Dec 16
SUVN-502	Neurotransmitter based	5-HT6 antagonist	NCT02580305	Suven Life Sciences	Sep 15	Jun 17
T-817 MA	Neuroprotective	Neurotrophic agent	NCT02079909	Toyama	Mar 14	Mar 17
Telmisartan	Neuroprotective	PPAR-gamma agonist	NCT02085265	Sunnybrook Health Sciences Centre	Mar 14	Aug 18
UB-311	Anti-amyloid	Monoclonal antibody	NCT02551809	United Neuroscience	Oct 15	Jan 18
VX-745	Neuroprotective	P38 mitogen-activated protein kinase inhibitor	NCT02423200	EIP Pharma	Apr 15	Jan 16
			NCT02423122	EIP Pharma	Apr 15	Sep 16

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BACE, beta-site amyloid precursor protein cleaving enzyme. GM-CSF, granulocyte-macrophage colony-stimulating factor; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme; hUCB-MSCs, human umbilical cord-derived mesenchymal stem cells; IVIG, intravenous immunoglobulin; NMDA, N-methyl-D-aspartate; PDE, phosphodiesterase; PPAR, peroxisome proliferator-activated receptor.

NOTE. Forty-six agents in 52 phase II clinical trials currently ongoing (active, not recruiting and active, recruiting) as of January 4, 2016 according to clinicaltrials.gov.

Table 3
Agents currently in phase I of development and their mechanism of action (as of 1/4/2016)

Agent	Agent mechanism class	Mechanism of action	Clinicaltrials.gov ID	Sponsor	Start date	Estimated end date
AADvac1	Anti-tau	Monoclonal antibody directed at Tau epitope	NCT02031198	Axon Neuroscience	Jan 14	Sep 17
ABT-957	Neuroprotective	Calpain inhibitor	NCT02220738	AbbVie	Sep 14	Jun 16
			NCT02573740	AbbVie	Nov 15	Nov 16
Aducanumab	Anti-amyloid	Monoclonal antibody	NCT01677572	Biogen	Oct 12	Oct 19
			NCT02434718	Biogen	May 15	Jul 17
Allopregnanolone injection	Neuroprotective	GABA receptor modulator	NCT02221622	University of Southern California	Aug 14	Mar 17
BI 409306	Neurotransmitter based	PDE 9A inhibitor	NCT02392468	Boehringer Ingelheim	Apr 15	Oct 16
Bisnorcymserine (BNC)	Neurotransmitter based	Butyrylcholinesterase inhibitor	NCT01747213	National Institute on Aging (NIA)	Nov 12	Jul 17
Crenezumab	Anti-amyloid	Monoclonal antibody	NCT02353598	Genentech	Feb 15	Sep 17
CT1812	Anti-amyloid	Sigma-2 receptor modulator; reduces amyloid toxicity	NCT02570997	Cognition Therapeutics	Sep 15	Jun 16
GC021109	Anti-inflammatory, neuroprotective	Anti-inflammatory	NCT02386306	GliaCure	Feb 15	Oct 15
Insulin Aspart Intranasal	Metabolic	Insulin	NCT02462161	Wake Forest School of Medicine	May 15	Dec 16
JNJ-54861911	Anti-amyloid	BACE inhibitor	NCT02360657	Janssen	Feb 15	Sep 15
KHK6640	Anti-amyloid	Amyloid aggregation inhibitor	NCT02127476	Kyowa Hakko Kirin Pharma	Jul 14	Feb 17
			NCT02377713	Kyowa Hakko Kirin Pharma	Mar 15	Dec 16
Lorazepam	Neurotransmitter based	Benzodiazepam	NCT01780519	Mayo Clinic	Jan 13	Sep 16
Lu AF20513	Anti-amyloid	Monoclonal antibody	NCT02388152	H. Lundbeck A/S	Mar 15	Dec 16
LY2599666 + Solanezumab	Anti-amyloid	Monoclonal antibody combination	NCT02614131	Eli Lilly and Company	Dec 15	Jul 17
LY3002813	Anti-amyloid	Monoclonal antibody	NCT01837641	Eli Lilly and Company	May 13	Sep 16
LY3202626	Anti-amyloid	Undisclosed mechanism	NCT02323334	Eli Lilly and Company	Dec 14	Feb 16
MEDI1814	Anti-amyloid	Monoclonal antibody	NCT02036645	AstraZeneca	Feb 14	Oct 16
NGP 555	Anti-amyloid	Gamma-secretase modulator	NCT02534480	NeuroGenetic Pharmaceuticals	Mar 15	Nov 15
Oxaloacetate	Metabolic	Mitochondrial enhancer	NCT02593318	University of Kansas Medical Center	Oct 15	Oct 17
PF-06751979	Anti-amyloid	Undisclosed mechanism	NCT02509117	Pfizer	Jul 15	Jul 16
S-Equol	Neuroprotective	Estrogen receptor beta agonist	NCT02142777	University of Kansas Medical Center	Jul 14	Dec 16
Telmisartan	Neuroprotective	PPAR-gamma agonist	NCT02471833	Emory University	Apr 15	Mar 18
TPI-287	Anti-tau	Microtubule protein modulator	NCT01953705	University of California, San Francisco	May 14	Mar 19

Abbreviations: BACE = beta-site amyloid precursor protein cleaving enzyme; GABA = gamma-aminobutyric acid; PDE = phosphodiesterase; PPAR = peroxisome proliferator-activated receptor.
NOTE. Twenty-four agents in 27 phase I clinical trials currently ongoing (active, not recruiting, and active, recruiting) as of January 4, 2016, according to clinicaltrials.gov.

Table 4
Percent of trials with specific biomarkers included (this calculation is based on the number of trials in which the inclusion of biomarkers is described)

	% of trials	
Biomarker	Phase III	Phase II
1. CSF amyloid	27.7	25
2. CSF tau	22.2	21.1
3. FDG-PET	19.4	11.5
4. vMRI	25	15.3
5. Plasma amyloid	8.3	5.7
6. Plasma tau	0	3.8
7. Amyloid PET	22.2	9.6
8. Tau PET	2.7	0

cancer has identified more putative targets. Greater insight into AD pathophysiology may lead to more target identification and more opportunities to develop mechanistically informed treatments.

The AD drug-development pipeline has amyloid beta-protein production or removal as it major focus. Across all phases, 56% of DMTs have an amyloid-related target. Monoclonal antibodies and BACE inhibitors comprise the two most developed pathways in the current pipeline. Monoclonal antibody approaches have instituted two major changes in drug development based on experiences with the failure of bapineuzumab: (1) patient populations with more mild disease are now the focus of trials [12]; (2) amyloid imaging or CSF Aβ measures are performed at baseline to insure that patients have the target pathology for antiamyloid therapies [13,14]. BACE inhibitors have included measures of CSF Aβ to demonstrate target engagement and show that the putative goal of reduction is being achieved [15]. Demonstration of target engagement early in the development process makes it more likely—without proving—that clinical benefits may follow long-term therapy [16].

Tau is a relatively unexploited target with only four agents in the pipeline devoted to tau-related pathophysiology. The availability of tau imaging and the consistent relationships shown between tau signals on imaging and the clinical state of the individual indicate that tau is an important target for drug development and that tau imaging may serve as a useful biomarker to help guide drug development [17–20]. Tau protein is being targeted in trials of experimental therapies for tauopathies including frontotemporal dementia and progressive supranuclear palsy, and learnings from these trials may inform treatment of tau pathology in AD.

Thirty-eight percent of DMTs are small molecule agents that address neuroprotection or metabolic targets such as insulin resistance or PPAR-gamma–related mechanisms. These approaches are more well represented in phase II than phase III and suggest that the repertoire of targets is broadening for agents in the AD pipeline.

Symptomatic agents represent an important part of the AD drug-development pipeline. Improvement in cognitive and behavioral symptoms is a major goal of treatment and is achieved only partially by current therapies. There are 25 symptomatic cognitive enhancers or neuropsychiatric agents in the current pipeline comprising 27% of the entire drug-development pipeline. Symptomatic treatments are especially well represented in phase II where they comprise 33% of all agents at that stage of development. These agents enhance cholinergic signaling or capitalize on noncholinergic serotonergic, sigma-1, phosphodiesterase, or N-methyl-D-asparate (NMDA) mechanisms.

There is increasing recognition that combination therapies may be warranted to address the complex biology of AD [21]. Combinations have found success in other complex diseases such as cancer, tuberculosis, and human immunodeficiency virus infections. There are few examples in the AD pipeline of combination of agents in trials; ALZT-OP1a/1b is a combination approach at phase III, simvastatin/l-arginine/tetrahydrobiopterin is being assessed at phase II; and LY2599666 plus solanezumab is being tested in phase I. In addition to these pharmacodynamics combinations, AVP-786 is a pharmacokinetic combination of dextromethorphan and the CYP2D6 inhibitor, quinidine, used to elevate levels of dextromethorphan. Overall, combinations comprise a limited aspect of the AD drug-development pipeline and represent an important future direction of drug development.

Currently, DMTs spend relatively little time in phase II (average 49 weeks) and involve a small number of patients per trial arm (average 67). Given the 100% failure rate of DMTs in phase III, more thorough exploration of these agents in phase II may benefit drug-development programs and the likelihood of phase III success.

Biomarkers play an increasingly important role in AD drug development. The demonstration that approximately 25% of patients included in trials of clinical-diagnosed AD do not have elevated levels of brain amyloid when studied with amyloid imaging indicated that use of biomarkers was critical in identifying a population with the target pathology in trials of antiamyloid agents and that have an accurate diagnosis for inclusion of trials of other agents [13,14]. Nearly, all current trials of antiamyloid agents require positive amyloid imaging at baseline to insure accurate diagnosis and include amyloid imaging as an outcome to determine the effect of the therapeutic intervention on the brain plaque burden. Target engagement biomarkers are now more commonly used in drug-development programs such as those for BACE inhibitors to show that a biological effect has been achieved and that clinical effects could reasonably be expected. CSF measurements of amyloid and tau, volumetric MRI, and amyloid PET are used approximately equally commonly in DMT programs; no consensus on a single biomarker or combination of biomarkers as

optimal to meet regulatory expectations for biomarker data has emerged.

Of trials across all phases of AD drug development, 74% are completely or partially sponsored by the biopharmaceutical industry. Given the prominent role of industry in AD drug development, legislative incentives to attract the pharmaceutical and biotechnology industries to AD may be one of the means of enhancing the number of candidate agents entering the AD pipeline. Increased federal funding to augment the small number of trial sponsored by NIH (9% with total or partial NIH funding) might also enhance the pipeline. Funding for basic science through NIH or venture capital support of biotechnology companies is needed to identify new targets and generate new candidate therapies. Similarly, new strategies in drug development including more emphasis on demonstrating target engagement in early stage development and use of adaptive designs to support clinical trials decision making may accelerate the drug development process and decrease the number of late-stage failures of agents in the pipeline.

This analysis is based on a review of clinicaltrials.gov and is subject to the limitations of that database. While inclusive of all trials in the United States and many non-US countries, it may not include all trials being conducted in other countries and the list of drugs we discuss may not be comprehensive from an international perspective. In addition, not all phase I trials are included on clinicaltrials.gov, especially when they are conducted in non-US phase I units, and we may underestimate the total number of agents being assessed in phase I. There is sometimes a lag in listing trials on clinicaltrials.gov, and the lists included here may not be fully comprehensive for the time window assessed. These limitations will affect some details of the analysis but not the overall view of the landscape of AD drug development.

In summary, the AD drug-development pipeline is modest in size and strikingly smaller than very active areas of experimental therapeutics such as cancer. The phase I candidate pool is particularly small and bodes poorly for a compelling set of agents to be advanced to phase II and III. Amyloid is the most common pharmaceutical target, reflecting the greater understanding of the pathophysiology of this peptide. Symptomatic agents are making progress toward treatment of both cognitive and behavioral symptoms of AD. Biomarkers are being integrated into DMT development programs. Every source of compounds including academic medical centers, NIH, philanthropic funders, biotechnology, and pharmaceutical companies should be attracted to AD drug development to create a larger pipeline and a greater chance of success of AD drug development.

Acknowledgments

There was no external funding for the study.

RESEARCH IN CONTEXT

1. Systematic Review: Drug development for Alzheimer's disease (AD) proceeds through three phases (I, II, III). By assessing the number of agents in each phase as recorded on clinicaltrials.gov, one can determine current AD drug development activity to assess how many agents are being studied, the success of the research, and how the number of new drugs can be increased.
2. Interpretation: Our data show that there are 93 drugs in development for treatment of AD. There are more drugs in phase II (45) than in phase III (24) or phase I (24). The small number of phase I compounds suggest that there is insufficient drug discovery activity to supply new agents for testing in clinical trials.
3. Future directions: This review of the AD drug-development pipeline provides insight into the state of AD drug development and encourages review of how best to amplify the drug discovery/development ecosystem.

References

[1] Alzheimer's Association. 2015 Alzheimer's disease facts and figures. Alzheimers Dement 2015;11:332–84.
[2] Sosa-Ortiz AL, Acosta-Castillo I, Prince MJ. Epidemiology of dementias and Alzheimer's disease. Arch Med Res 2012;43:600–8.
[3] Cummings JL, Morstorf T, Zhong K. Alzheimer's disease drug-development pipeline: Few candidates, frequent failures. Alzheimers Res Ther 2014;6:37.
[4] Tasneem A, Aberle L, Ananth H, Chakraborty S, Chiswell K, McCourt BJ, et al. The database for aggregate analysis of ClinicalTrials.gov (AACT) and subsequent regrouping by clinical specialty. PLoS One 2012;7:e33677.
[5] Berk C, Paul G, Sabbagh M. Investigational drugs in Alzheimer's disease: current progress. Expert Opin Investig Drugs 2014;23:837–46.
[6] Cummings JL. Controversies in Alzheimer's disease drug development. Int Rev Psychiatry 2008;20:389–95.
[7] Wiendl H, Elger C, Forstl H, Hartung HP, Oertel W, Reichmann H, et al. Gaps between aims and achievements in therapeutic modification of neuronal damage ("Neuroprotection"). Neurotherapeutics 2015; 12:449–54.
[8] Appleby BS, Nacopoulos D, Milano N, Zhong K, Cummings JL. A review: treatment of Alzheimer's disease discovered in repurposed agents. Dement Geriatr Cogn Disord 2013;35:1–22.
[9] Mangialasche F, Solomon A, Winblad B, Mecocci P, Kivipelto M. Alzheimer's disease: clinical trials and drug development. Lancet Neurol 2010;9:702–16.
[10] Tufts Center for the Study of Drug Development. Clinical success rates for new cancer drugs double while more enter testing. In: Kenneth I, Kaitin P, eds. Impact Report. Boston, MA: Tufts University; 2013. p. 1–4.
[11] Mullard A. 2015 FDA drug approvals. Nat Rev Drug Discov 2016; 15:73–6.

[12] Doody RS, Thomas RG, Farlow M, Iwatsubo T, Vellas B, Joffe S, et al. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. N Engl J Med 2014;370:311–21.

[13] Salloway S, Sperling R, Fox NC, Blennow K, Klunk W, Raskind M, et al. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. N Engl J Med 2014;370:322–33.

[14] Sevigny J, Suhy J, Chiao P, Chen T, Klein G, Purcell D, et al. Amyloid PET screening for enrichment of early-stage Alzheimer disease clinical trials: Experience in a Phase 1b clinical trial. Alzheimer Dis Assoc Disord 2016;30:1–7.

[15] Menting KW, Claassen JA. Beta-secretase inhibitor; a promising novel therapeutic drug in Alzheimer's disease. Front Aging Neurosci 2014; 6:165.

[16] Cook D, Brown D, Alexander R, March R, Morgan P, Satterthwaite G, et al. Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework. Nat Rev Drug Discov 2014;13:419–31.

[17] Brier MR, Gordon B, Friedrichsen K, McCarthy J, Stern A, Christensen J, et al. Tau and Abeta imaging, CSF measures, and cognition in Alzheimer's disease. Sci Transl Med 2016;8:338ra66.

[18] Gordon BA, Friedrichsen K, Brier M, Blazey T, Su Y, Christensen J, et al. The relationship between cerebrospinal fluid markers of Alzheimer pathology and positron emission tomography tau imaging. Brain 2016;139:2249–60.

[19] Ossenkoppele R, Schonhaut DR, Scholl M, Lockhart SN, Ayakta N, Baker SL, et al. Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease. Brain 2016;139:1551–67.

[20] Scholl M, Lockhart SN, Schonhaut DR, O'Neil JP, Janabi M, Ossenkoppele R, et al. PET Imaging of tau deposition in the aging human brain. Neuron 2016;89:971–82.

[21] Perry D, Sperling R, Katz R, Berry D, Dilts D, Hanna D, et al. Building a roadmap for developing combination therapies for Alzheimer's disease. Expert Rev Neurother 2015;15:327–33.