Alzheimer's & Dementia: Translational Research & Clinical Interventions 3 (2017) 367-384

Review Article

Alzheimer's disease drug development pipeline: 2017

Jeffrey Cummings[a,*], Garam Lee[a], Travis Mortsdorf[b], Aaron Ritter[a], Kate Zhong[c]

[a]Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, NV, USA
[b]Touro University Nevada, Henderson, NV, USA
[c]Global Alzheimer Platform, Washington, D.C., USA

Abstract

Introduction: There is an urgent need to develop new treatments for Alzheimer's disease (AD) and to understand the drug development process for new AD therapies.

Methods: We assessed the agents in the AD pipeline as documented in clinicaltrials.gov for phase I, phase II, and phase III, accessed 1/5/2017.

Results: There are 105 agents in the AD treatment development pipeline, of which 25 agents are in 29 trials in phase I, 52 agents are in 68 trials in phase II, and 28 agents are in 42 trials in phase III. Seventy percent of drugs in the AD pipeline are disease-modifying therapies (DMTs). Fourteen percent are symptomatic cognitive enhancers, and 13% are symptomatic agents addressing neuropsychiatric and behavioral changes (2% have undisclosed mechanisms). Most trials are sponsored by the biopharmaceutical industry. Trials include patients with preclinical AD (cognitively normal with biomarker evidence of AD), prodromal AD (mild cognitive symptoms and biomarker evidence of AD), and AD dementia. Biomarkers are included in many drug development programs particularly those for DMTs. Thirteen of 46 phase II DMT trials have amyloid imaging as an entry criterion, and 10 of 28 phase III trials incorporate amyloid imaging for diagnosis and entry. A large number of participants are needed for AD clinical trials; in total, 54,073 participants are required for trials spanning preclinical AD to AD dementia. When compared with the 2016 pipeline, there are eight new agents in phase I, 16 in phase II, and five in phase III.

Discussion: The AD drug development pipeline has 105 agents divided among phase I, phase II, and phase III. The trials include a wide range of clinical trial populations, many mechanisms of action, and require a substantial number of clinical trial participants. Biomarkers are increasingly used in patient identification and as outcome measures, particularly in trials of DMTs.

Keywords: Alzheimer's disease; Phase I; Phase II; Phase III; Biomarkers; Preclinical AD; Prodromal AD; AD dementia

Alzheimer's disease (AD) is increasing rapidly in frequency as the world's population ages and more people enter the major risk period for this age-related disorder. From the 5.3 million US citizens affected now, the number of victims will increase to 13 million or more by 2050; worldwide the total number of affected individuals will increase to a staggering 100 million [1]. The cost of care in the US, currently more than $200 billion annually, will grow to an unsupportable $1 trillion annually by 2050 [1].

New therapies are urgently needed to treat affected patients and to prevent, defer, slow the decline, or improve the symptoms of AD. It has been estimated that the overall frequency of the disease would be decreased by nearly 50% if the onset of the disease could be delayed by 5 years [2]. Symptomatic

J.C. has provided consultation to AbbVie, Acadia, Actinogen, Alzheon, Anavex, Avanir, Axovant, Bracket, Eisai, Genentech, Lilly, Lundbeck, MedAvante, Merck, Orion, Otsuka, Pfizer, QR, Roche, Suven, and Takeda Pharmaceutical and assessment companies. T.M., G.L., and A.R. have no disclosures. K.Z. is an employee of the Global Alzheimer Platform.

*Corresponding author. Tel.: +1-702-483-6029; Fax: +1-702-722-6584.

E-mail address: cumminj@ccf.org

http://dx.doi.org/10.1016/j.trci.2017.05.002

treatments are drugs aimed at cognitive enhancement or control of neuropsychiatric symptoms and typically work through neurotransmitter mechanisms; disease-modifying therapies or treatments (DMTs) are agents that prevent, delay, or slow progression and target the underlying pathophysiologic mechanisms of AD [3].

To understand the progress of drug development, describe the timelines regarding when drugs could become available, and interrogate the current drug development approaches for AD treatments, we examined the AD drug development pipeline as currently revealed in clinicaltrials.gov. We present our findings as a means of understanding and ultimately improving AD drug development. This paper continues the themes developed in our 2016 pipeline report [4] and impacts the understanding of the likelihood of reaching the national goal of having meaningful therapy for AD by 2025 [5].

1. Methods

Clinicaltrials.gov includes a comprehensive list of all clinical trials of AD and describes the trial features in text form. The "Common Rule" governing clinicaltrials.gov was updated in 2016 [6,7]. Registration is mandated for all trials from sponsors with an Investigational New Drug or Investigational New Device. Trials must be submitted to the site within 21 days of the enrollment of the first trial participant. Results must be submitted to clincaltrials.gov within 12 months of completion of final data collection for the prespecified primary outcome measures; clinicaltrials.gov can be regarded as a comprehensive resource for the study of clinical trials governed by the US Food and Drug Administration (FDA) or the National Institutes of Health (NIH). Not all non-US trials are registered on clinicaltrials.gov—especially phase I trials. We also cannot attest to compliance with the rule governing clinicaltrials.gov, and some agents may not be registered or sponsors may not adhere to required timelines.

We examined clinicaltrials.gov as of January 5, 2017. We captured all trials of all agents in phases I, II, and III. In a comprehensive database, we entered the trial title, beginning date, projected end date, calculated duration, number of subjects planned to be enrolled, number of arms of the study (usually a placebo arm and one or more treatment arms with different doses of the experimental agent), whether a biomarker was described, and sponsorship by a biopharma company, NIH, academic medical center, "other" entity such as a consortium or a philanthropic organization, or a combination of the aforementioned sponsors. We included trials that were recruiting, active but not recruiting (e.g., trials that have completed recruiting and are continuing as the efficacy or safety of the agent is being determined), enrolling by invitation, and not yet recruiting. We did not include trials listed as completed, terminated, suspended, or withdrawn. Information on these trials or the reasons for suspension or termination is often incomplete. The choice of types of trials included was informed by our intention of understanding the currently active pipeline and to know what agents could evolve in the near term. We did not include trials of nonpharmacologic therapeutic approaches such as devices, cognitive therapies, and medical food. We did not include trials of biomarkers.

The mechanism of action (MOA) 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 and could not be identified in the literature. We grouped the mechanisms into symptomatic agents or DMTs. We divided the symptomatic agents into those that are putative cognitive enhancing agents or those that address neuropsychiatric and behavioral symptoms. DMTs were divided into those that target amyloid-related mechanisms, those that have tau-related MOAs, and those with "other" mechanisms such as anti-inflammatory MOAs, growth factors, or metabolic effects. Stem cell therapies were included in the "other" category.

2. Results

2.1. Overview

Fig. 1 provides an overview of all agents currently in the AD pipeline. The circles reveal the stages of development (I, II, and III), the colors pertain to the MOA of the agent, and the shape denotes the population in which the agent is being tested (normal volunteers, cognitive normal at-risk individuals, prodromal AD, and AD dementia).

In all, there are 105 agents in the pipeline as shown on clinicaltrials.gov, of which 25 are agents in 29 trials in phase I, 52 agents are in 68 trials in phase II, and 28 agents are in 42 trials in phase III. Across all stages, 70% are DMTs, 14% are symptomatic cognitive enhancers, 13% are symptomatic agents addressing neuropsychiatric and behavioral changes, and 2% have undisclosed MOAs.

Of all trials, 65.5% are sponsored by the biopharma industry, 16.6% by Academic Medical Centers, 3.6% by Academic Medical Center-NIH collaborations, and 10.8% by the collaborations between consortiums/philanthropic organizations and one or more of the following: biopharma, NIH, and Academic Medical Centers. One trial is sponsored by NIH, one trial by biopharma-NIH collaboration, and one trial by a biopharma-NIH-Academic Medical Center collaboration.

2.2. Phase I

Phase I first-in-human trials are generally conducted in healthy volunteers unless they are assessing immunotherapies where the potential long-term modification of the immune system makes participation of normal controls impermissible. These trials generally progress from single ascending dose trials where increasing doses are administered once in supervised settings to assess tolerability and establish a maximum tolerated dose to multiple ascending dose trials where individuals receive doses for 14 to

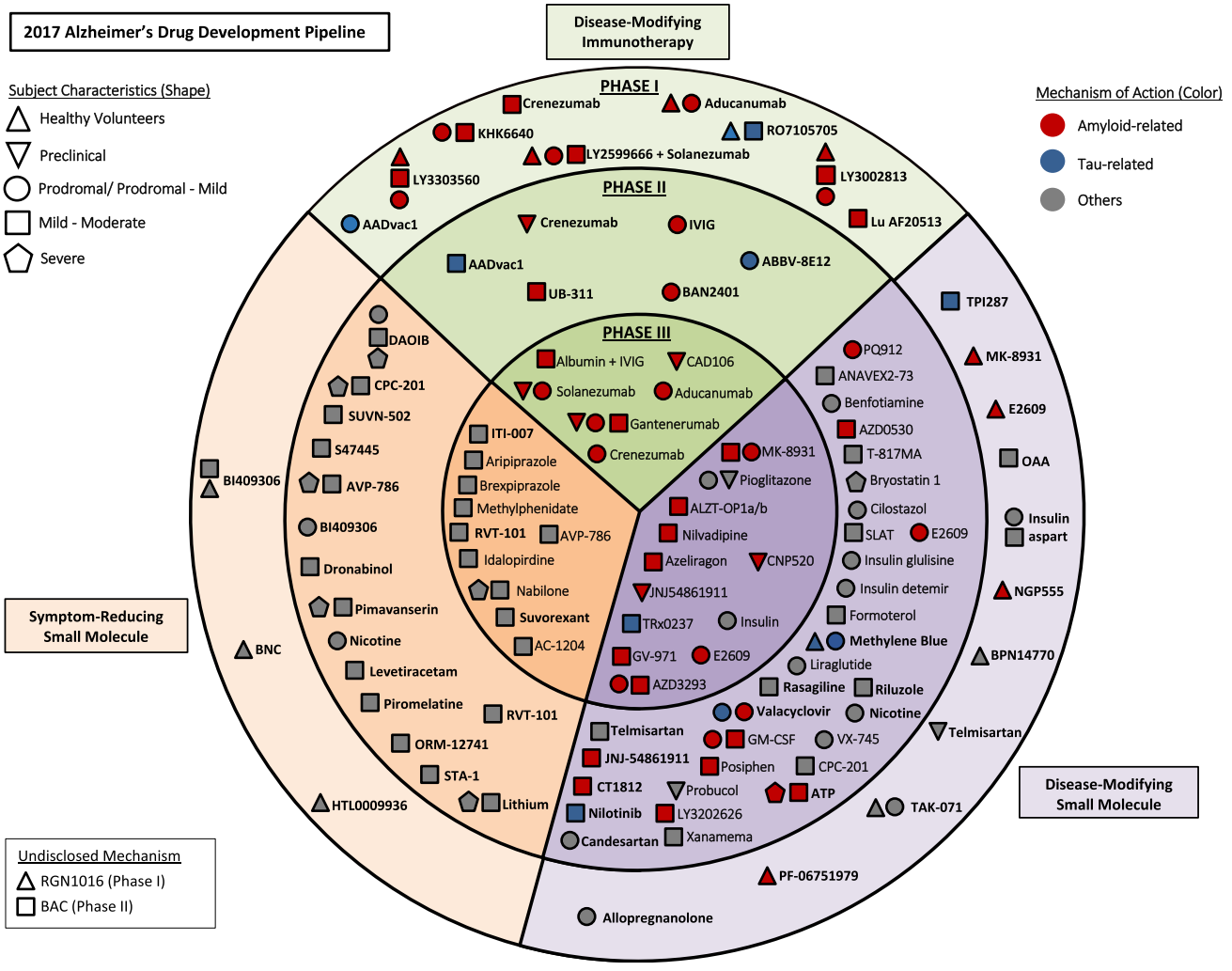

Fig. 1. Agents in clinical trials for the treatment of Alzheimer's disease in 2017 (from clinicaltrials.gov accessed 1/5/2017). Abbreviations: ATP, adenosine triphosphate; BNC, bisnorcymserine; GM-CSF, granulocyte-macrophage colony-stimulating factor; OAA, oxaloacetate; IVIG, intravenous immunoglobulin; SLAT, simvastatin + L-arginine + tetrahydrobiopterin.

28 days [8–10]. Single and multiple ascending dose studies typically include cohorts of 6 to 12 individuals assigned asymmetrically to drug or placebo (e.g., four on placebo and eight on drug in a 12-person cohort). The goal of phase I trials is to assess the safety and tolerability of the agent, identify the doses to be advanced to phase II, and document the pharmacokinetics (PK) of the drug (e.g., half-life, time to maximum serum concentration [T-max], maximum serum concentration for each dose [C-max], bioavailability, dose-blood level linearity, etc). PK studies are conducted in animals before phase I but must be repeated in the first-in-human setting to establish the PK characteristics specific to men and women. Food effects on drug absorption and drug-drug interactions are also assessed in phase I studies. A cohort of healthy elderly is often included to assess the effect of age on PK parameters. In phase I/II studies, a cohort of individuals with AD may be included.

Of the 24 agents whose MOA was revealed in phase I in 2017 (Fig. 1; Table 1), 12 were directed at amyloid-related targets including eight immunotherapies, three had tau-related MOAs, and nine had other mechanisms including four symptomatic cognitive enhancers. Overall, there were 20 DMTs and four symptomatic agents in phase I. The MOA was not revealed for one agent.

Phase I trials were on average 755 days in duration (recruitment and treatment period) and involved 68 patients in each trial.

2.3. Phase II

Phase II trials advance the agents from phase I to trial populations of patients with AD. The goal of these trials is to establish preliminary efficacy based on a biomarker outcome, a clinical measure, or a combination of clinical and biomarker outcomes [11,12]. Phase IIa trials concentrate on efficacy, and phase IIb trials further refine dosing decisions about the number of doses to be advanced to phase III. Of the 68 trials in phase II of the

Table 1
Agents currently in phase I of Alzheimer's disease drug development (as of 1/5/2017)

Agent	Agent mechanism class	Mechanism of action	Clinicaltrials.gov identifier	Status	Sponsor	Start date	Estimated end date
AC-1204	Metabolic	Ketogenic agent	NCT01741194*	Active, not recruiting	Accera	Mar-13	Oct-17
Aducanumab	Anti-amyloid	Monoclonal antibody	NCT02484547	Recruiting	Biogen	Sep-15	Feb-22
			NCT02477800	Recruiting	Biogen	Aug-15	Feb-22
Albumin + immunoglobulin	Anti-amyloid	Polyclonal antibody	NCT01561053*	Recruiting	Grifols	Mar-12	Dec-16
ALZT-OP1a + ALZT-OP1b	Anti-amyloid, anti-inflammatory	Anti-amyloid combination, inhibits neuroinflammatory response	NCT02547818	Recruiting	AZTherapies	Sep-15	Mar-18
Aripiprazole	Neurotransmitter based	Atypical anti-psychotic (dopamine partial agonist)	NCT02168920	Recruiting	Otsuka	Jun-14	Jul-17
AVP-786	Neurotransmitter based	Mixed transmitter effect; agitation therapy	NCT02442765	Recruiting	Avanir	Sep-15	Jul-18
			NCT02446132	Recruiting	Avanir	Dec-15	Jul-19
AZD3293 (LY3314814)	Anti-amyloid	BACE1 inhibitor	NCT02245737*	Recruiting	AstraZeneca, Eli Lilly	Sep-14	Aug-19
			NCT02783573	Recruiting		Jul-16	Apr-21
			NCT02972658	Not yet recruiting		Mar-17	Jul-20
Brexpiprazole (OPC-34712)	Neurotransmitter based	Atypical anti-psychotic (dopamine partial agonist)	NCT01862640	Recruiting	Otsuka, Lundbeck	Jul-13	Jun-17
			NCT01922258	Recruiting	Otsuka, Lundbeck	Sep-13	Jun-17
CAD106	Anti-amyloid	Amyloid vaccine	NCT02565511*	Recruiting	Novartis, Amgen, NIA, Alzheimer's Association	Nov-15	Aug-23
CNP520	Anti-amyloid	BACE inhibitor					
Crenezumab	Anti-amyloid	Monoclonal antibody	NCT02670083	Recruiting	Roche/Genentech	Mar-16	Jul-21
E2609	Anti-amyloid	BACE inhibitor	NCT02956486	Recruiting	Eisai, Biogen	0ct-16	Jun-20
Gantenerumab	Anti-amyloid	Monoclonal antibody	NCT02051608	Active, not recruiting	Roche	Mar-14	Nov-19
			NCT01224106	Active, not recruiting	Roche	Nov-10	Dec-19
			NCT01760005*	Active, not recruiting	Washington University, Eli Lilly, Roche, NIA, Alzheimer's Association	Dec-12	Dec-19
Idalopirdine (Lu AE58054)	Neurotransmitter based	5-HT6 antagonist	NCT02079246	Recruiting, Extension	Lundbeck	Apr-14	Oct-17
			NCT02006654	Active, not recruiting	Lundbeck	Mar-14	Mar-17
Insulin (humulin)	Metabolic	Metabolic agent	NCT01767909*	Recruiting	University of Southern California, NIA, ATRI, Wake Forest University	Sep-13	Feb-17
ITI-007	Neurotransmitter based	5-HT2A antagonist, dopamine receptor modulator	NCT02817906	Recruiting	Intra-Cellular Therapies, Inc.	Jun-16	Aug-18
JNJ-54861911	Anti-amyloid	BACE inhibitor	NCT02569398*	Recruiting	Janssen	Nov-15	May-23
Methylphenidate	Neurotransmitter based	Dopamine reuptake inhibitor	NCT02346201	Recruiting	Johns Hopkins, NIA	Oct-15	Aug-20

(*Continued*)

Table 1
Agents currently in phase I of Alzheimer's disease drug development (as of 1/5/2017) (*Continued*)

Agent	Agent mechanism class	Mechanism of action	Clinicaltrials.gov identifier	Status	Sponsor	Start date	Estimated end date
MK-8931 (verubecestat)	Anti-amyloid	BACE inhibitor	NCT01953601	Active, not recruiting	Merck	Nov-13	Mar-21
			NCT01739348*	Active, not recruiting	Merck	Nov-12	Jul-19
MK-4305 (suvorexant)	Neurotransmitter based	Dual orexin receptor antagonist	NCT02750306	Recruiting	Merck	May-16	Jul-17
Nabilone	Neurotransmitter based	Cannabinoid (receptor agent)	NCT02351882*	Recruiting	Sunnybrook Health Sciences Centre	Jan-15	Dec-17
Nilvadipine	Anti-Amyloid	Calcium channel blocker	NCT02017340	Active, not recruiting	St. James' Hospital Ireland, Alzheimer Europe, Archer Pharmaceuticals	Oct-12	Dec-17
Pioglitazone	Metabolic	PPAR-gamma agonist, anti-amyloid effect	NCT02284906	Recruiting, Extension	Takeda	Feb-15	Apr-21
			NCT01931566	Active, not recruiting	Takeda	Aug-13	Jul-19
RVT-101 (intepirdine)	Neurotransmitter based	5-HT6 antagonist	NCT02585934	Recruiting	Axovant Sciences	Oct-15	Oct-17
			NCT02586909	Recruiting, Extension	Axovant Sciences	Apr-16	Jun-18
Sodium Oligo-mannurarate (GV-971)	Anti-amyloid	Anti-amyloid agent	NCT02293915	Recruiting	Shanghai Greenvalley Pharmaceutical	Apr-14	May-17
Solanezumab	Anti-amyloid	Monoclonal antibody	NCT01760005*	Active, not recruiting	Washington University, Eli Lilly, Roche, NIA, Alzheimer's Association	Dec-12	Dec-19
			NCT02008357	Recruiting	Eli Lilly, ATRI	Feb-14	Oct-20
			NCT01127633	Active, not recruiting, Extension	Eli Lilly	Dec-10	Feb-17
			NCT01900665	Active, not recruiting	Eli Lilly	Jul-13	Feb-17
			NCT02760602	Recruiting	Eli Lilly	Jun-16	Apr-21
TRx0237	Anti-tau	Tau protein aggregation inhibitor	NCT02245568	Recruiting, Extension	TauRx Therapeutics	Aug-14	Sept-17
TTP488 (azeliragon)	Anti-amyloid, anti-inflammatory	Anti-amyloid RAGE antagonist	NCT02080364	Recruiting	vTv Therapeutics	Apr-15	Jan-19
			NCT02916056	Not yet recruiting		Dec-16	Nov-20

Abbreviations: ATRI, Alzheimer's Therapeutic Research Institute; BACE, β-site amyloid precursor protein cleaving enzyme; NIA, National Institute on Aging; PPAR, peroxisome proliferator-activated receptor; RAGE, receptor for advanced glycation end products.

NOTE. Twenty-eight agents in 42 phase III clinical trials as of January 5, 2017 according to clinicaltrials.gov.

*Phase II/III trials. Bolded = new entries into the 2017 phase III pipeline.

Table 2
Agents currently in phase II of Alzheimer's disease drug development (as of 1/5/2017)

Agent	Agent mechanism class	Mechanism of Action	Clinicaltrials.gov identifier	Status	Sponsor	Start date	Estimated end date
AADvac1	Anti-tau	Monoclonal antibody	NCT02579252	Recruiting	Axon Neuroscience	Dec-15	Feb-19
ABBV-8E12	Anti-tau	Monoclonal antibody	NCT02880956	Recruiting	AbbVie	Oct-16	Mar-21
ATP	Anti-amyloid	Inhibits amyloid misfolding and toxicity	NCT02279511	Active, not recruiting	Fundació Clínic per la Recerca Biomèdica, Spain	Nov-14	Nov-16
AD-SVF cells	Regenerative	AD-SVF cell infusion	NCT02912169*	Recruiting	Ageless Regenerative Institute	Nov-15	Dec-17
ANAVEX 2-73	Neuroprotective	Sigma-1 receptor agonist	NCT02244541	Active, not recruiting	Anavex Life Sciences	Dec-14	Oct-16
			NCT02756858	Recruiting, extension		Mar-16	Nov-18
Atomoxetine	Anti-amyloid	Adrenergic uptake inhibitor, SNRI	NCT01522404	Active, not recruiting	Emory University, NIA	Mar-12	Dec-17
AVP-786	Neurotransmitter based	Mixed transmitter effect	NCT02534038	Recruiting	Avanir	Oct-15	Mar-18
AZD0530 (saracatinib)	Anti-amyloid	Kinase inhibitor	NCT02167256	Active, not recruiting	Yale University, ATRI, AstraZeneca	Dec-14	Dec-17
BAC	Undisclosed	Undisclosed mechanism	NCT02886494	Not yet recruiting	Charsire Biotechnology	Nov-16	Nov-19
			NCT02467413	Not yet recruiting	Charsire Biotechnology, A2 Healthcare Taiwan Corporation	Mar-16	Dec-17
BAN2401	Anti-amyloid	Monoclonal antibody	NCT01767311	Recruiting	Eisai	Dec-12	Jul-18
Benfotiamine	Metabolic	Antioxidant	NCT02292238	Recruiting	Burke Medical Research Institute, Columbia University, NIA, ADDF	Nov-14	Nov-19
BI409306	Neuroprotective	Phosphodiesterase 9A inhibitor	NCT02240693	Recruiting	Boehringer Ingelheim	Jan-15	Oct-17
			NCT02337907	Recruiting	Boehringer Ingelheim	Jan-15	Oct-17
Bryostatin 1	Neuroprotective	Protein kinase C modulator	NCT02431468	Active, not recruiting	Neurotrope Bioscience	Jul-15	May-17
Candesartan	Neuroprotective, anti-inflammatory	Angiotensin receptor blocker	NCT02646982	Recruiting	Emory University	Jun-16	Sep-21
CB-AC-02 (Placenta derived-MSCs)	Regenerative	Stem cell therapy	NCT02899091*	Not yet recruiting	CHA Biotech Co.	Sep-16	Jun-18
Cilostazol	Neuroprotective	Phosphodiesterase 3 antagonist	NCT02491268	Recruiting	National Cerebral and Cardiovascular Center, Japan	Jul-15	Jul-18
CPC-201	Neuroprotective	Cholinesterase inhibitor + peripheral cholinergic antagonist	NCT02549196	Recruiting	Chase Pharmaceuticals	Oct-15	Dec-16
			NCT02434666	Active, not recruiting, Extension	Chase Pharmaceuticals	Jan-15	Dec-16
			NCT02860065	Not yet recruiting	Chase Pharmaceuticals	Sep-16	Jun-17
Crenezumab	Anti-amyloid	Monoclonal antibody	NCT01998841	Recruiting	Genentech, NIA, Banner Alzheimer's Institute	Dec-13	Sep-20
CT1812	Anti-amyloid	Sigma-2 receptor modulator	NCT02907567*	Recruiting	Cognition Therapeutics	Sep-16	May-17
DAOIB	Neurotransmitter based	NMDA enhancer	NCT02103673	Recruiting	Chang Gung Memorial Hospital, Taiwan	Feb-14	Sep-17
			NCT02239003	Recruiting	Chang Gung Memorial Hospital, Taiwan	Jan-12	Dec-17
Dronabinol	Neurotransmitter based	CB1 and CB2 endocannabinoid receptor partial agonist	NCT02792257	Not yet recruiting	Mclean Hospital, Johns Hopkins University	Aug-16	Dec-20
E2609	Anti-amyloid	BACE inhibitor	NCT02322021	Recruiting	Eisai, Biogen	Nov-14	Jan-18

(*Continued*)

Table 2
Agents currently in phase II of Alzheimer's disease drug development (as of 1/5/2017) (*Continued*)

Agent	Agent mechanism class	Mechanism of Action	Clinicaltrials.gov identifier	Status	Sponsor	Start date	Estimated end date
Formoterol	Neuroprotective, anti-inflammatory	β-2 adrenergic receptor agonist	NCT02500784	Recruiting	Palo Alto Veterans Institute for Research, Mylan, Alzheimer's Association	Jan-15	Jul-16
hUCB-MSCs	Regenerative	Stem cell therapy	NCT02054208*	Recruiting	Medipost	Feb-14	Feb-18
			NCT01547689*	Active, not recruiting	Affiliated Hospital to Academy of Military Medical Sciences, China	Mar-12	Dec-16
			NCT02513706	Not yet recruiting	South China Research Center	May-16	Oct-19
			NCT02672306*	Not yet recruiting	South China Research Center	May-16	Oct-19
			NCT02833792	Recruiting	Stemedica Cell Technologies	Jun-16	Jun-18
Insulin detemir (intranasal)	Metabolic	Increases insulin signaling in the brain	NCT01595646	Active, not recruiting	Wake Forest School of Medicine, Alzheimer's Association	Nov-11	Mar-17
Insulin glulisine	Metabolic	Increases insulin signaling in the brain	NCT02503501	Recruiting	HealthPartners Institute	Aug-15	Sep-17
JNJ-54861911	Anti-amyloid	BACE inhibitor	NCT02406027	Active, not recruiting, Extension	Janssen	Jul-15	Oct-22
Levetiracetam	Neurotransmitter based	Anticonvulsant	NCT02002819	Recruiting	University of California, San Francisco	Jun-14	Dec-17
Liraglutide	Metabolic	Glucagon-like peptide 1 receptor agonist	NCT01843075	Recruiting	Imperial College London	Jan-14	Mar-19
Lithium	Neurotransmitter based	Ion channel modulator	NCT02129348	Recruiting	New York State Psychiatric Institute, NIA	Jun-14	Apr-19
LY3202626	Anti-amyloid	BACE Inhibitor	NCT02791191	Recruiting	Eli Lilly	Jun-16	Aug-18
Methylene blue	Anti-tau	Tau inhibitor; neuronal stimulant	NCT02380573	Recruiting	Texas Alzheimer's Research and Care Consortium	Jul-15	Jul-18
NewGam 10% IVIG	Anti-amyloid	Polyclonal antibody	NCT01300728	Active, not recruiting	Sutter Health	Jan-11	Nov-17
Nicotine	Neurotransmitter based	Nicotinic acetylcholine receptor agonist	NCT02720445	Not yet recruiting	University of Southern California, NIA, ATRI, Vanderbilt University	Dec-16	Dec-19
Nilotinib	Anti-tau	Tyrosine kinase inhibitor	NCT02947893	Not yet recruiting	Georgetown University	Nov-16	Mar-18
ORM-12741	Neurotransmitter based	Alpha-2c adrenergic receptor antagonist	NCT02471196	Recruiting	Orion Corporation, Janssen	Jun-15	Jul-17
Pimavanserin	Neurotransmitter based	5-HT2A inverse agonist	NCT02035553	Active, not recruiting	Acadia	Nov-13	Nov-16
			NCT02992132	Recruiting	Acadia	Nov-16	Jun-19
Piromelatine	Neurotransmitter based	Melatonin receptor agonist; 5-HT 1A and 1D receptor agonist	NCT02615002	Recruiting	Neurim Pharmaceuticals	Nov-15	Mar-18
Posiphen	Anti-amyloid	Selective inhibitor of APP production	NCT02925650*	Not yet recruiting	QR Pharma, ADCS	Dec-16	Dec-18
PQ912	Anti-amyloid, anti-inflammatory	Glutaminyl-peptide cyclotransferase inhibitor	NCT02389413	Recruiting	Probiodrug AG, Julius Clinical, VU University Medical Center, Amsterdam	Mar-15	Mar-17

(*Continued*)

Table 2
Agents currently in phase II of Alzheimer's disease drug development (as of 1/5/2017) (*Continued*)

Agent	Agent mechanism class	Mechanism of Action	Clinicaltrials.gov identifier	Status	Sponsor	Start date	Estimated end date
Probucol	Neuroprotective, anti-inflammatory	Anti-hyperlipidemic	NCT02707458*	Not yet recruiting	Douglas Mental Health University Institute, Weston Brain Institute, McGill University	Apr-16	May-18
Rasagiline	Neuroprotective	Monoamine oxidase B inhibitor	NCT02359552	Recruiting	The Cleveland Clinic	Feb-15	May-17
Riluzole	Neuroprotective	Glutamate receptor antagonist; glutamate release inhibitor	NCT01703117	Recruiting	Rockefeller University	Apr-13	Nov-18
RVT-101	Neurotransmitter based	5-HT6 antagonist	NCT02910102	Recruiting	Axovant Sciences	Oct-16	Sep-17
S47445	Neurotransmitter based	AMPA receptor agonist; nerve growth factor stimulant	NCT02626572	Active, not recruiting	Servier	Feb-15	Dec-17
Sargramostim (GM-CSF)	Anti-amyloid	Granulocyte colony stimulator; amyloid removal	NCT01409915	Recruiting	University of Colorado, Denver, The Dana Foundation	Mar-11	Jan-17
			NCT02667496	Recruiting	Sanofi, NIA	Nov-16	Apr-18
Simvastatin + L-Arginine + Tetrahydrobiopterin (SLAT)	Neuroprotective	HMG-CoA reductase inhibitor and antioxidant	NCT01439555	Recruiting	University of Massachusetts, Worcester	Nov-11	Dec-16
STA-1	Neuroprotective, anti-inflammatory	Antioxidant properties of echinascoside	NCT01255046	Not yet recruiting	Sinphar Pharmaceuticals	Dec-15	Dec-18
SUVN-502	Neurotransmitter based	5-HT6 antagonist	NCT02580305	Recruiting	Suven Life Sciences	Sep-15	Jun-17
T-817 MA	Neuroprotective	Neurotrophic agent	NCT02079909	Active, not recruiting	Toyama Chemical, ADCS	Mar-14	Mar-17
Telmisartan	Neuroprotective, anti-inflammatory	Angiotensin II receptor blocker, PPAR-gamma agonist	NCT02085265	Recruiting	Sunnybrook Health Sciences Centre, ADDF	Mar-14	Aug-18
UB-311	Anti-amyloid	Monoclonal antibody	NCT02551809	Recruiting	United Neuroscience	Oct-15	Dec-17
Valacyclovir	Anti-amyloid, Anti-tau	Antiviral agent	NCT02997982	Recruiting	Umea University	Dec-16	Dec-17
VX-745	Neuroprotective, anti-inflammatory	P38 mitogen-activated protein kinase inhibitor	NCT02423200	Active, not recruiting	EIP Pharma	Apr-15	Nov-16
			NCT02423122	Active, not recruiting	EIP Pharma	Apr-15	Sep-16
Xanamema	Neuroprotective	Blocks 11-HSD1 enzyme activity, decreasing cortisol in brain	NCT02727699	Not yet recruiting	Actinogen Medical, ICON Clinical Research	Jun-16	Aug-18

Abbreviations: ADCS, Alzheimer's Disease Cooperative Study; ADDF, Alzheimer's Drug Discovery Foundation; AD-SVF, adipose-derived stromal vascular fraction; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ATP, adenosine triphosphate; ATRI, Alzheimer's Therapeutic Research Institute; BACE, β-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; NIA, National Institute on Aging; NMDA, N-methyl-D-aspartate; PPAR, peroxisome proliferator-activated receptor; SNRI, serotonin-norepinephrine reuptake inhibitors.

NOTE. Fifty-two agents in 68 phase II clinical trials currently ongoing as of January 5, 2017 according to clinicaltrials.gov.

*Phase I/II trials. Bolded = new entries into the 2017 phase II pipeline.

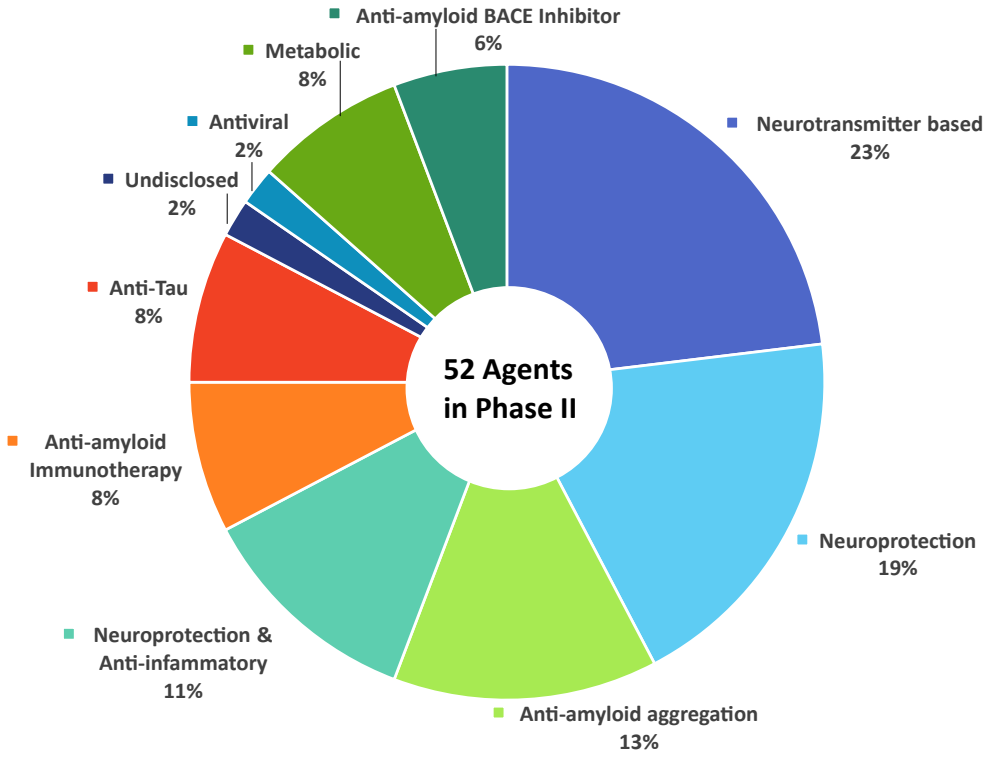

Fig. 2. Mechanisms of action of agents in phase II. Abbreviation: BACE, β-site amyloid precursor protein cleaving enzyme.

AD pipeline, 21 included patients with prodromal or prodromal and mild AD, 26 were trials for mild-moderate AD, one included patients with prodromal or mild-moderate AD, and one trial was for mild-moderate or severe AD. Of the symptomatic trials, 10 were for mild-moderate AD and six were for mild-moderate or severe AD.

On average, phase II trials were 1140 days in duration (recruitment plus exposure period) and involved 151 patients in each trial.

Of the 52 agents in the 68 trials, there were 36 DMTs, eight cognitive enhancing agents, seven drugs for behavioral symptoms, and one agent with an unknown MOA (Fig. 1; Table 2). Among the DMTs, 14 addressed amyloid targets, four involved tau-related targets, one addressed both amyloid and tau-related targets, and 17 had other MOAs (e.g., metabolic, or anti-inflammatory). The DMTs include six immunotherapies (four addressing amyloid and two addressing tau). Of the DMTs, 17 are repurposed agents approved for use in another indication. There are seven trials involving stem cell programs.

Of the drugs with amyloid targets, there were three β-site amyloid precursor protein cleaving enzyme (BACE) inhibitors, four immunotherapies, and eight anti-aggregation agents. Fig. 2 shows the MOAs of agents in phase II.

2.4. Phase III

Phases II and III trials are often called "learn" and "confirm" trials, respectively, with phase III intended to confirm effects observed in phase II in larger populations treated for longer periods of time [11,13]. In addition to providing crucial efficacy data, phase III trials also provide exposure data on larger numbers of patient-days essential to establishing the safety and tolerability of the candidate therapy.

Of the 28 agents in the 42 trials, there were 18 DMTs, three cognitive enhancing agents, and seven drugs for behavioral symptoms. Among the DMTs, 15 addressed amyloid targets, one involved a tau-related target, and two had a metabolic MOA. The DMTs include six immunotherapies (all addressing amyloid). Of the DMTs, four are repurposed agents approved for use in another indication. Of the drugs with amyloid targets, there were five BACE inhibitors, six immunotherapies, and four anti-aggregation agents. Table 3 shows the agents currently in phase III of AD drug development. Fig. 3 shows the MOAs of agents in phase III and Fig. 4 shows an illustration of the drug mechanism of phase III agents and the proposed biology of AD.

Among the DMT trials, there were five prevention trials enrolling cognitively normal participants at high risk for developing AD in the course of the trials; 14 trials of patients with prodromal AD (those with minimal cognitive symptoms and a biomarker indicative of AD-related brain changes) or prodromal/mild AD; and nine trials of patients with mild-moderate AD.

On average, phase III trials involved 1012 patients and were 1677 days in duration (including the recruitment and the treatment period). When divided by MOA, DMT trials were 1948 days long (945.84 treatment days) and included 1212 patients. Cognitive enhancer trials were 1114 days

Table 3
Agents currently in phase III of Alzheimer's disease drug development (as of 1/5/2017)

Agent	Agent mechanism class	Mechanism of Action	Clinicaltrials.gov identifier	Status	Sponsor	Start date	Estimated end date
AADvac1	Anti-tau	Monoclonal antibody directed at Tau epitope	NCT02031198	Active, not recruiting	Axon Neuroscience	Jan-14	Dec-16
Aducanumab	Anti-amyloid	Monoclonal antibody	NCT01677572	Active, not recruiting	Biogen	Oct-12	Oct-19
			NCT02434718	Active, not recruiting	Biogen	May-15	Dec-16
			NCT02782975	Active, not recruiting	Biogen	May-16	Nov-16
Allopregnanolone injection	Regenerative	GABA receptor modulator	NCT02221622	Recruiting	University of Southern California, NIA	Aug-14	Jun-17
BI409306	Neurotransmitter based	Phosphodiesterase 9A inhibitor	NCT02392468	Recruiting	Boehringer Ingelheim	Apr-15	May-17
Bisnorcymserine (BNC)	Neurotransmitter based	Butyrylcholinesterase inhibitor	NCT01747213	Recruiting	NIA	Nov-12	Jul-17
BPN14770	Neuroprotective	Negative allosteric modulator of phosphodiesterase 4D	NCT02840279	Recruiting	Tetra Discovery Partners	Jun-16	Dec-16
			NCT02648672	Recruiting	Tetra Discovery Partners	Dec-15	Apr-16
Crenezumab	Anti-amyloid	Monoclonal antibody	NCT02353598	Recruiting	Genentech	Feb-15	May-17
E2609	Anti-amyloid	BACE Inhibitor	NCT02859207	Not yet recruiting	Eisai, Biogen	Aug-16	Jan-17
HTL0009936	Neurotransmitter based	Muscarinic M1 receptor agonist	NCT02546310	Recruiting	Heptares Therapeutics	Sep-15	Sep-16
Insulin Aspart Intranasal	Metabolic	Increases insulin signaling in the brain	NCT02462161	Recruiting	Wake Forest School of Medicine, NIA, General Electric	May-15	Dec-16
KHK6640	Anti-amyloid	Amyloid aggregation inhibitor	NCT02127476	Active, not recruiting	Kyowa Hakko Kirin Pharma	Jul-14	Apr-17
hMSCs	Regenerative	Stem cell therapy	NCT02600130	Recruiting	Longeveron LLC	Jan-16	Oct-19
Lu AF20513	Anti-amyloid	Polyclonal antibody	NCT02388152	Recruiting	H. Lundbeck A/S	Mar-15	May-17
LY2599666 + solanezumab	Anti-amyloid	Monoclonal antibody combination	NCT02614131	Active, not recruiting	Eli Lilly and Company	Dec-15	Sep-17
LY3002813	Anti-amyloid	Monoclonal antibody	NCT01837641	Active, not recruiting	Eli Lilly and Company	May-13	Jan-17
			NCT02624778	Recruiting	Eli Lilly and Company	Dec-15	Jun-20
LY3303560	Anti-amyloid	Monoclonal antibody	NCT02754830	Recruiting	Eli Lilly and Company	Apr-16	Apr-17
MK-8931 (verubecestat)	Anti-amyloid	BACE Inhibitor	NCT02910739	Recruiting	Merck	Oct-16	Apr-17
NGP 555	Anti-amyloid	Gamma-secretase modulator	NCT02537938	Recruiting	NeuroGenetic Pharmaceuticals	Jan-16	Oct-16
Oxaloacetate (OAA)	Metabolic	Mitochondrial enhancer	NCT02593318	Recruiting	University of Kansas Medical Center	Oct-15	Oct-17
PF-06751979	Anti-amyloid	Undisclosed mechanism	NCT02793232	Recruiting	Pfizer	Jun-16	Jan-17
RGN1016	Undisclosed	Undisclosed mechanism	NCT02820155	Recruiting	National Taiwan University	Jun-16	Feb-17
RO7105705	Anti-tau	Anti-tau antibody	NCT02820896	Recruiting	Genentech	Jun-16	May-17

(*Continued*)

Table 3
Agents currently in phase III of Alzheimer's disease drug development (as of 1/5/2017) (*Continued*)

Agent	Agent mechanism class	Mechanism of Action	Clinicaltrials.gov identifier	Status	Sponsor	Start date	Estimated end date
TAK-071	Neurotransmitter based	Muscarinic M1 receptor modulator	NCT02769065	Recruiting	Takeda	May-16	Mar-17
Telmisartan	Neuroprotective, anti-inflammatory	Angiotensin II receptor blocker, PPAR-gamma agonist	NCT02471833	Recruiting	Emory University	Apr-15	Mar-18
TPI-287	Anti-tau	Microtubule protein modulator	NCT01966666	Active, not recruiting	University of California, San Francisco	May-14	Nov-17

Abbreviations: BACE, β-site amyloid precursor protein cleaving enzyme; GABA, gamma-aminobutyric acid; hMSCs, mesenchymal stem cells; NIA, National Institute on Aging; PPAR, peroxisome proliferator-activated receptor.
NOTE. Twenty-five agents in 29 phase I clinical trials currently ongoing as of January 5, 2017 according to clinicaltrials.gov. Bolded = new entries into the 2017 phase I pipeline.

long (215.81 treatment days) and involved 1044 patients. Trials of drugs for behavioral symptoms are 1146 days long (113.61 treatment days) and included 372 patients. For all DMTs, the average duration of therapy is 135 weeks; the average period from trial initiation to primary completion date (final data collection date for primary outcome measure) is 246 weeks. This indicates that 111 weeks (>2 years) is the average anticipated recruitment time. On average, prevention trials recruiting cognitively normal individuals at risk for AD are 363 weeks in duration; trials entering patients with prodromal/prodromal-mild AD are 278 weeks in duration; and trials for patients with mild-moderate AD are 231 weeks in duration. Anticipated recruitment periods for these three types of trials are 134 weeks, 105 weeks, and 107 weeks, respectively.

2.5. Participant numbers

Recruitment is the slowest and most expensive aspect of clinical trials [14]. The period of recruitment may exceed the period of treatment in the clinical trial cycle. The total number of participants needed to populate all clinical trials for AD is large. Table 4 shows the number of participants needed for all current prevention trials, phase I, phase II, and phase III trials.

2.6. Biomarkers

Biomarkers have many roles in clinical trials including identifying patients for trials and verifying diagnosis, assessing target engagement and providing proof of pharmacology, serving as outcomes for DMT trials, and assessing side effects (e.g., monitoring amyloid-related imaging abnormalities [ARIAs] observed with some immunotherapies) [14–17]. ARIA has emerged as a concern in several major immunotherapy development programs–bapineuzumab, gantenerumab, and aducanumab. Although largely asymptomatic, these changes can lead to permanent neurologic sequelae and will be a focus of research once the efficacy of the immunotherapies is established. Preliminary evidence suggests that longer dose titration periods may decrease the risk of ARIAs [18].

Not all trial descriptions in clinicalrials.gov note if biomarkers are used. Table 5 shows the biomarkers used as outcome measures in current phase II and phase III AD clinical trials as included in the federal website. Of the 28 phase III DMT trials, 10 trials use amyloid positron emission tomography (PET) as an entry criterion, two use cerebrospinal fluid (CSF) amyloid, and two use either amyloid PET or CSF amyloid. Thirteen out of 46 phase II DMT trials used amyloid-PET as an entry criterion.

2.7. Comparison to 2016 pipeline

In any 1-year period, there is relatively little movement in the AD pipeline. Compared to 2016, there are eight new agents in phase I, 16 in phase II, and five in phase III. Of the new agents in phase II, three of the 16 were previously

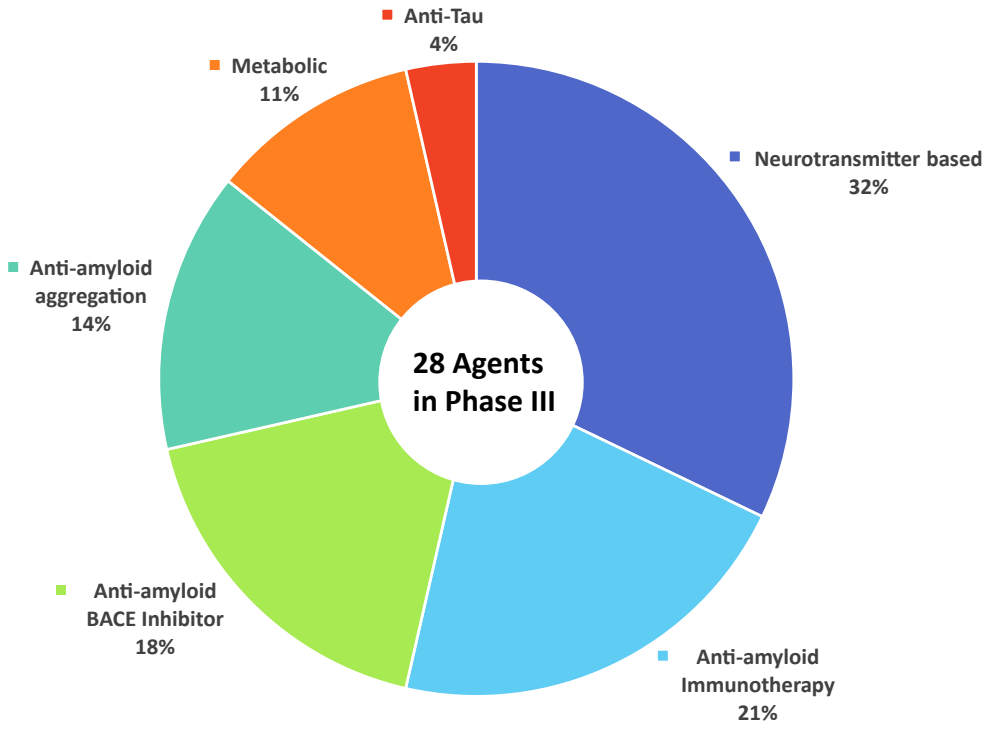

Fig. 3. Mechanisms of action of agents in phase III. Abbreviation: BACE, β-site amyloid precursor protein cleaving enzyme.

present in phase I (AADvac1, CT1812, and LY3202626). Of the new agents in phase III, two of the five were previously noted in phase II (crenezumab and E2609).

Agents can appear in phase II without having been listed in phase I because the phase I study was not done in the US and was not registered on clinicaltrials.gov or because they are repurposed agents that had the PK and dosing established through trials for a non-AD indication [15,19,20]. Rarely, a repurposed agent can enter directly into phase III without a phase II trial. In the AD pipeline, there are 18 repurposed agents in phase II and nine in phase III.

Seven agents were listed in phase II in 2016 and are not listed in phase I, II, or III in 2017. These agents have at least temporarily exited the drug development pipeline. Four trials for the following agents were completed in 2016 but are not listed in the 2017 pipeline: exenatide, PXT00864, RO4602522, and RPh201. Two trials were terminated (MK-7622 and PF-05212377), and the trial status for metformin changed to "unknown" because it has not been updated for more than 2 years on clinicaltrials.gov.

One agent (masitinib) was listed in phase III in 2016 and is not listed in phase I, II, or III in 2017. Its trial status changed to "unknown" because it has not been updated on clinicaltrials.gov since 2013. Development of this agent has been at least temporarily interrupted.

Candidate agents that are no longer evident in the pipeline may have failed to demonstrate efficacy in well-conducted trials, they may have failed to show efficacy in trials whose features suggest the trials were not well conducted, or there may be industry reasons for halting the program (e.g., insufficient funding, reprioritization of agents in development, change in company business agenda, and management decision after assessment of the competitive landscape) [21].

3. Discussion

There is a modest pipeline of drugs in development for AD. Most candidate therapies are DMTs (70% across all phases), and the remainder are symptomatic agents directed at cognitive enhancement (14%) or treatment of neuropsychiatric symptoms (13%) and agents with undisclosed MOAs (2%). This closely resembles the pipeline as it appeared in 2016 where 73% were DMTs, 18% cognitive enhancers, and 9% psychotropic agents [4]. There are eight new agents in phase I, 16 in phase II, and five in phase III. From the 2016 pipeline, several agents have exited and not yet reappeared including six in phase I, seven in phase II, and one in phase III. Leuco-methylthioninium (LMTM) (or TRx0237) derived from methylene blue and addressing tau aggregation completed its phase III trials in 2016 and failed to meet prespecified outcomes of the trial [22]; however, its open-label extension study is listed as ongoing.

The shortcomings of clinicaltrials.gov as a database are important to recognize when considering the data presented here. Not all phase I trials, especially those conducted outside the US, may be registered, and our phase I data may underestimate the number of phase I candidates. Trials are required to be registered within 21 days of entering the first patient into

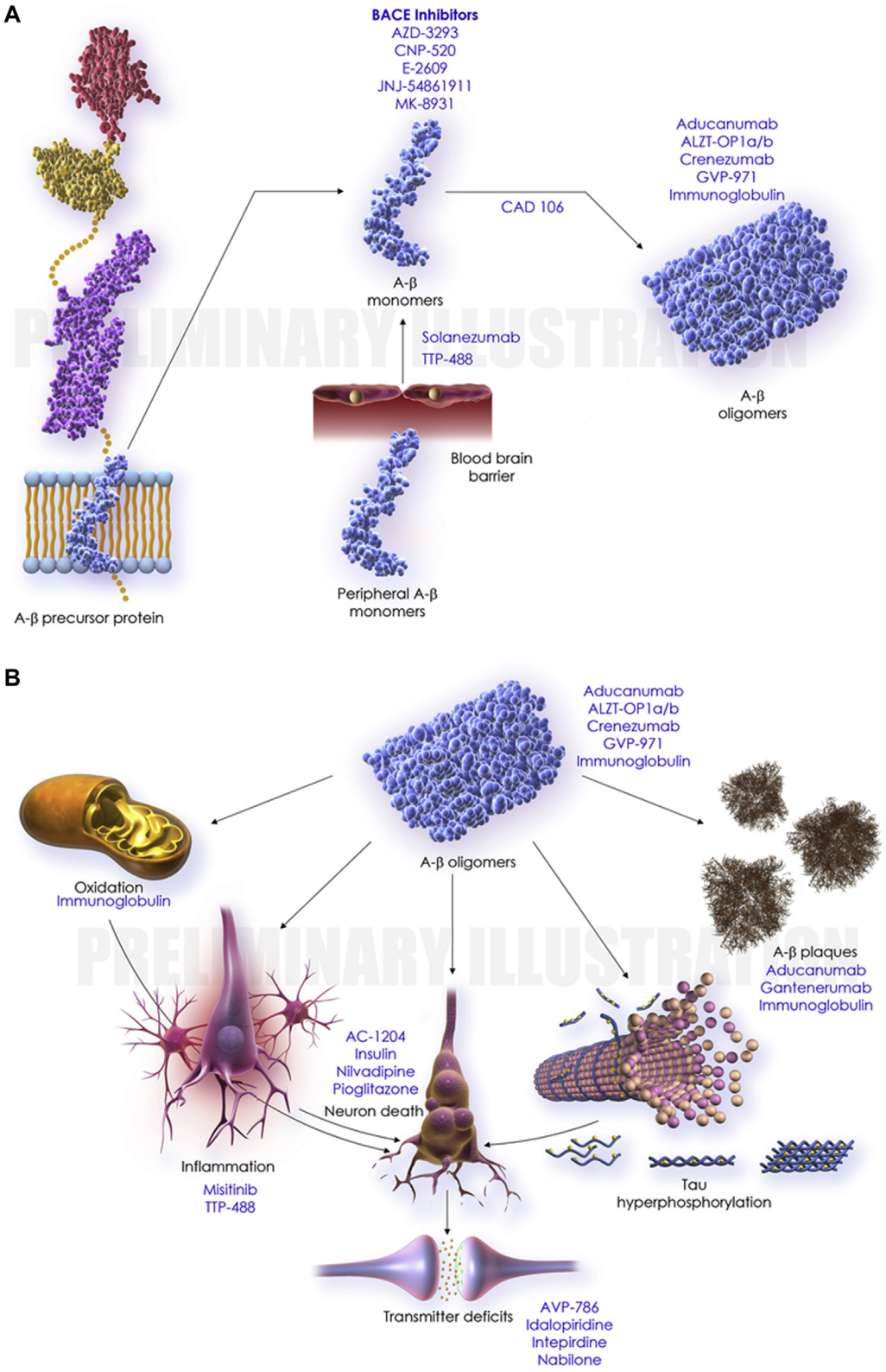

Fig. 4. Illustration of drug mechanism (phase III agents) and the proposed biology of Alzheimer's disease. (A) Amyloid cascade. (B) Downstream pathophysiology. Abbreviation: BACE, β-site amyloid precursor protein cleaving enzyme.

Table 4
Number of participants needed for AD clinical trials

Participant type	Phase I	Phase II	Phase III	Total
Healthy volunteers	864	120	0	984
Preclinical AD	66	323	7850	8239
Prodromal/prodromal-mild AD	597	3877	17,535	22,009
Mild-moderate AD	626	4528	17,099	22,253
Severe AD	0	568	20	588
Total	2153	9416	42,504	54,073

Abbreviation: AD, Alzheimer's disease.

Table 5
Biomarkers as outcome measures in phase II and phase III trials for agents in the Alzheimer's disease drug development pipeline (clinicaltrials.gov; 1/5/2017)

	N of trials (%)	
Biomarker	Phase III	Phase II
CSF amyloid	12 (28.6)	17 (25.0)
CSF tau	13 (31.0)	16 (23.5)
FDG-PET	5 (11.9)	10 (14.7)
vMRI	9 (21.4)	6 (8.8)
Plasma amyloid	4 (9.5)	5 (7.4)
Plasma tau	0	1 (1.5)
Amyloid PET	13 (31.0)	6 (8.8)
Tau PET	1 (2.4)	0

Abbreviations: CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; PET, positron emission tomography; vMRI, volumetric magnetic resonance imaging.

the trial [7], but not all sponsors meet this deadline. The data provided may not represent the entire universe of AD drug development [23]. We stopped entering new data into our database at a time that allowed submission, peer review, and publication; the data presented are a few months out-of-date (data collection stopped January 5, 2017). Nevertheless, the FDA Modernization Act requires all trials to be registered and the International Committee of Medical Journal Editors requires trials to be registered to be eligible for publication [24]. The clinicaltrials.gov database is acceptably comprehensive—the most complete of any existing database—and a sound basis for drawing conclusions about AD drug development with the caveats mentioned here.

Phase I is not the only source of compounds for phases II and III. Agents repurposed from other indications may have MOAs worthy of exploration in AD. Antihypertensive agents, statins, anti-inflammatory agents, calcium channel blockers, and agents with many other MOAs have been proposed as drugs with effects possibly useful in treating AD and can enter AD drug development pipelines at phase II or phase III [15,19,20]. Psychiatric agents are commonly developed in non-AD populations (e.g., major depressive disorder, schizophrenia) before being assessed in AD patients. Safety, tolerability, PK, and dosing observations of phase I may be available from studies conducted for the initial indication. Thus, the phase I observations provided here may not entirely forecast the compounds available for phase II and phase III. Nevertheless, the intellectual property challenges of repurposed compounds such as short-patent life limit biopharma interest in these agents, and only a modest number of repurposed agents are represented in the AD drug development pipeline (18 in phase II and six in phase III). The small number of phase I compounds is a concern for the overall health of the AD drug development pipeline.

A striking observation derived from these data is the long recruitment period anticipated for phase III DMTs. The anticipated recruitment period is often longer than the treatment period, and in many cases, these planned recruitment goals are not met [25,26]. Prevention trials require more time to recruit than prodromal trials (133.5 weeks and 105.4 weeks, respectively) and mild-moderate AD trials (106.9 weeks). Slow recruitment is among the greatest challenges to efficiency of AD drug development [14]. This observation underlies recent efforts in the AD drug development arena to advance new methods for patient recruitment including electronic engagement of potential participants, creation of registries of candidate subjects, and providing transportation, neighborhood vans, and insurance-based referral mechanisms to facilitate subject recruitment and shorten drug development timelines [27,28].

A daunting conclusion from this review of clinicaltrials.gov is the large number of participants required to conduct the trials. Registered preclinical AD trials will require 8239 participants; trials of prodromal or prodromal/mild populations require 22,009 participants; trials of mild to moderate AD dementia are forecasted to require 22,253 participants; and trials in severe AD dementia will require 588 participants. In total, 54,073 participants will be required to complete the current AD trials. Trial recruitment is among the slowest and most expensive of all aspects of clinical trial conduct. The recruitment of such large numbers of participants will represent a substantial challenge to the system, and reforms are necessary to accelerate clinical trials and enhance recruitment [27,28].

BACE inhibitors are among the most common classes of molecules in the AD pipeline. Currently, there are 10 phase II or phase III trials involving BACE inhibitors (Table 6). The pipeline for BACE inhibitors has emerged only recently largely because of the challenging structure-activity requirements for BACE inhibition; agents need to be large enough to block BACE's large active site, while at the same time, agents need to be small enough to pass through the blood-brain barrier and lipophilic enough to enter endosomes where BACE is active [29]. Advances in small-molecule screening approaches have helped overcome these challenges and facilitated the entry of a number of BACE inhibitors into the pipeline [30]. All the BACE inhibitors currently in phases II and III trials are small molecules that demonstrate favorable PK when administered orally. The published results of phase I testing in both healthy participants and AD populations have demonstrated robust (45%–95%) reductions in CSF amyloid β protein (Aβ) levels [31]. This degree of target engagement has not previously been documented with other anti-amyloid therapies leading some authors to posit that BACE inhibition represents the first true test of

Table 6
BACE inhibitors in clinical trials for AD

BACE inhibitors currently in phase II or III of development					
Agent (sponsor)	Clinicaltrials.gov identifier (trial name)	Phase	Population	Start date	Estimated end date
CNP520 (Novartis)	NCT02565511 (GENERATION)	II/III	Asymptomatic (homozygote *APOE* ε4/ε4)	11/2015	08/2023
E2609 (Eisai)	NCT02322021	II	MCI to moderate AD	11/2014	01/2018
	NCT02956486 (MISSION-AD1)	III	MCI to mild AD	10/2016	06/2020
JNJ54861911 (Janssen)	NCT02406027	II	MCI to mild AD	07/2015	10/2022
	NCT02569398	II/III	Preclinical (amyloid positive)	11/2015	05/2023
LY3202626 (Lilly)	NCT02791191 (NAVIGATE-AD)	II	Mild AD	06/2016	08/2018
LY3314814 (Lilly)	NCT02245737 (AMARANTH)	II/III	MCI to mild AD	9/2014	8/2019
	NCT02783573 (DAYBREAK ALZ)	III	Mild AD	7/2016	08/2021
Verubecestat (Merck)	NCT01739348 (EPOCH)	II/III	Mild to moderate AD	11/2012	06/2017

Abbreviations: AD, Alzheimer's disease; BACE, β-site amyloid precursor protein cleaving enzyme; MCI, mild cognitive impairment.

the amyloid hypothesis [32]. Based on strong biomarker data, some BACE inhibitors have bypassed phase II testing moving directly from phase I into phase III trials. As a result, little is known about the clinical efficacy or safety of long-term BACE inhibition. The first BACE inhibitor trial to be tested in phase III in an AD dementia population was recently terminated for the lack of efficacy [33]. Data from this and other studies will begin to answer the key questions regarding BACE inhibitors including when in the disease continuum should inhibition be started; what degree of amyloid inhibition is required for clinical benefit; does reduction in amyloid synthesis affect clinical progression; and are there unidentified safety concerns with long-term BACE inhibition?

Immunotherapies, especially monoclonal antibodies, are also well represented in the AD pipeline. There are currently 16 immunotherapy agents in 31 trials (Table 7). This includes aducanumab, solanezumab, crenezumab, gantenerumab, and BAN2401. Immunotherapies target a variety of epitopes of Aβ. Solanezumab targets soluble Aβ; this agent recently failed to show a drug-placebo difference in a phase III trial. It was terminated as a candidate therapy for AD dementia [34]. It continues in prevention trials. Aducanumab targets multiple Aβ species, has had an encouraging phase I/II trial, and is continuing in phase III [35].

President Obama articulated a goal of cure or meaningful treatment for AD by the year 2025 [5,36]. A recent analysis of AD drug development showed that it takes on average 13 years for a candidate treatment to move from laboratory to FDA review and 10 years for an agent to navigate the clinical development period from start of phase I to end of FDA review [37]. This means that under current circumstances, an agent must now be in phase II to possibly be approved by 2025 [5]. Although there are promising agents in the pipeline that could achieve this goal, it is clear that given the high rate of failure of AD drug development [38], the aim of having a repertoire of agents that could respond comprehensively and individually to a patient's clinical circumstances within the 2025 timeframe is in jeopardy.

There are many factors contributing to the currently low rate of success of drug development for AD. The understanding of the biology of AD is incomplete, the emphasis on testing single therapies where combinations may be required, the few candidates entering phase I, the lack of predictive validity of animal models, lack of efficacy of candidate therapies, and the emergence of unacceptable side effects all limit successful treatment development. When clinical trials are considered, the slowness of recruitment, lack, until recently, of tests for diagnostic confirmation, the requirement to globalize trials to achieve sufficient recruitment at the expense of data variability, and the heterogeneity of AD may all contribute to the lack of success in trials.

Biomarkers can contribute substantially to drug development success [39]. In AD, there are few biomarkers given the myriad of affected processes; there are only a small number of target engagement biomarkers capable of giving an early readout on proof of pharmacology; there are no surrogate markers known to predict the clinical outcome; and no validated outcome biomarkers have been shown to correlate with clinical outcomes in a trial in support of disease modification. These circumstances disadvantage AD drug development and increase the failure rates, especially for proposed DMTs.

Symptomatic agents are an important part of the AD drug development pipeline. There are four cognitive enhancing agents and no agents targeting behavioral symptoms in phase I clinical trials. Phase II has eight cognitive enhancing agents and seven behavioral agents in trials, whereas phase III has three cognitive enhancing agents and seven behavioral agents. Together there are 15 cognitive enhancers and 14 agents targeting neuropsychiatric symptoms in the pipeline. This comprises 27% of the AD drug development pipeline. Treatments for neuropsychiatric symptoms are more likely than other classes of drugs to enter the pipeline in phase II or III after they have been assessed in phase I with the intent of treating a primary psychiatric illness.

The solution to the problem of the few agents in the AD drug development pipeline, the many challenges facing candidate therapies, and the slow speed of testing drugs can be partially addressed by increased funding.

Table 7
Immunotherapies in clinical trials for AD (clinicaltrials.gov accessed 1/5/2017)

Agent	Sponsor	Target	Trial phase	Population
AADvac1	Axon Neuroscience	Anti-tau mAb	1	AD
AADvac1	Axon Neuroscience	Anti-tau mAb	2	Mild-moderate AD
ABBV-8E12	AbbVie	Anti-tau mAb	2	Early AD
Aducanumab	Biogen	mAb targeting multiple forms of Aβ	1	Healthy volunteers
Aducanumab	Biogen	mAb targeting multiple forms of Aβ	1	Prodromal-mild AD
Aducanumab	Biogen	mAb targeting multiple forms of Aβ	1	Mild-moderate AD
Aducanumab	Biogen	mAb targeting multiple forms of Aβ	3	Early AD
Aducanumab	Biogen	mAb targeting multiple forms of Aβ	3	Early AD
Albumin and immunoglobulin	Grifols	Polyclonal antibody targeting multiple forms of Aβ	3	Mild-moderate AD
BAN2401	Eisai	mAb targeting N terminal protofibrils	2	Early AD
CAD106	Novartis, NIA	$Aβ_{1–6}$, active vaccine	2	AD, at risk
Crenezumab	Genentech	mAb targeting soluble oligomer and fibrillar Aβ	1	Mild-moderate AD
Crenezumab	Genentech, NIA, Academic	mAb targeting soluble oligomer and fibrillar Aβ	2	ADAD
Crenezumab	Genentech	mAb targeting soluble oligomer and fibrillar Aβ	3	Prodromal-mild AD
Gantenerumab	Roche	mAb targeting aggregated Aβ	3	Mild AD
Gantenerumab	Roche	mAb targeting aggregated Aβ	3	Prodromal AD
Gantenerumab	Roche, Lilly, Alzheimer's Association	mAb targeting aggregated Aβ	2/3	AD, at risk
Solanezumab	Lilly, Roche, Alzheimer's Association	mAb targeting monomeric Aβ	2/3	AD, at risk
KH6640	Kyowa Hakko Kirin	mAb targeting aggregated Aβ	1	AD
Lu AF20513	Lundbeck		1	Mild AD
NewGam 10% IVIG	Sutter Health	Polyclonal antibody targeting multiple forms of Aβ	2	Amnestic MCI
LY2599666 & solanezumab	Lilly	Combination of BACE inhibitor and MAb targeting monomeric Aβ	1	MCI due to AD
LY3303560	Lilly		1	MCI due to AD-mild AD
LY30032813	Lilly		1	MCI due to AD
LY30032813	Lilly		1	Mild-moderate AD
RO7105705	Genentech	Anti-tau mAb	1	Mild-moderate AD
Solanezumab	Lilly	mAb targeting monomeric Aβ	3	Prodromal AD
Solanezumab	Lilly	mAb targeting monomeric Aβ	3	Preclinical AD
Solanezumab	Lilly	mAb targeting monomeric Aβ	3	AD
Solanezumab	Lilly	mAb targeting monomeric Aβ	3	Mild AD
UB-311	United Neuroscience	mAb targeting N terminal $Aβ_{1–14}$	2	Mild AD

Abbreviations: AD, Alzheimer's disease; ADAD, autosomal dominant Alzheimer's disease; mAb, monoclonal antibody; MCI, mild cognitive impairment Yes, the expansion is correct.; IVIG, intravenous immunoglobulin; NIA, National Institute on Aging.

The NIH is critically involved in addressing AD as one of the major challenges to human health that currently goes unchecked. Investment in basic research will assist in identifying more targets and candidate compounds, whereas investment in translational research can help support clinical trials and improve trial methods. Federal small business loans can help fund enterprising new approaches to drug treatment; academic medical centers can spin off biotech startups around promising tests, biomarkers, and drugs; and venture capital can help support startup through early phases of development until larger biopharma companies are ready to take agents through the final most expensive phases of clinical trials and FDA review. Philanthropy and innovative approaches such as venture philanthropy may help accelerate AD drug discovery and development funding [40]. Biopharma sponsors 65.5% of all clinical trials and is the major economic force for drug development.

All these financial instruments, however, are currently in place and are not sufficient to respond to the urgent need. New investment vehicles are needed, and some have been proposed such as private-federal bonds [41,42]. Medicare and insurance companies who stand to benefit from improved health of the elderly should be engaged in funding conversations. New types of collaborations (e.g., between NIH and biopharma companies and between two biopharma companies) and consortia (e.g., the Alzheimer's Disease Neuroimaging Initiative) are increasing the financial feasibility of bearing the expense of AD drug development and enhancing the chance of success.

The need is great, the challenges many, the rewards high: this is the condition of AD drug development. Monitoring

the AD drug development pipeline provides perspective on the success of the response to these challenges.

RESEARCH IN CONTEXT

1. Systematic review: Drug development for Alzheimer's disease (AD) proceeds through three phases (I, II, and 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 105 drugs in development for treatment of AD. There are more drugs in phase II (52) than in phase III (28) or phase I (25). The small number of phase I compounds suggests 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 can help guide new development programs.

References

[1] Alzheimer's Association. 2015 Alzheimer's disease facts and figures. Alzheimers Dement 2015;11:332–84.
[2] Alzheimer's Association. Changing the Trajectory of Alzheimer's Disease: How a Treatment by 2025 Saves Lives and Dollars. Chicago, IL: Alzheimer's Association; 2015.
[3] Cummings JL, Zhong K. Chapter 17-symptomatic cognitive enhancing agents A2-Wolfe. In: Michael S, ed. Developing Therapeutics for Alzheimer's Disease. Boston: Academic Press; 2016. p. 459–75.
[4] Cummings J, Morstorf T, Lee G. Alzheimer's drug development pipeline: 2016. Alzheimers Dement 2016;2:222–32.
[5] Cummings J, Aisen PS, DuBois B, Frolich L, Jack CR Jr, Jones RW, et al. Drug development in Alzheimer's disease: the path to 2025. Alzheimers Res Ther 2016;8:39.
[6] Hudson KL, Lauer MS, Collins FS. Toward a new era of trust and transparency in clinical trials. JAMA 2016;316:1353–4.
[7] Zarin DA, Tse T, Williams RJ, Carr S. Trial reporting in clinicaltrials.gov - the final rule. N Engl J Med 2016;375:1998–2004.
[8] Curry S, DeCory HH, Gabrielsson J. Phase I: the first opportunity for extrapolation from animal data to human exposure. In: Edwards LD, Fox AW, Stonier, eds. Principles and Practice of Pharmaceutical Medicine. Oxford, UK: Wiley-Blackwell; 2011. p. 84–106.
[9] Kelley J. Principles of CNS Drug Development: From Test Tube to Patient. Oxford, UK: Wiley-Blackwell; 2009.
[10] Norfleet E, Gad SC. Phase I clinical trials. In: Gad CS, ed. Clinical Trials Handbook. New York, New York: John Wiley & Sons, Inc.; 2009. p. 245–54.
[11] Gray JA, Fleet D, Winblad B. The need for thorough phase II studies in medicines development for Alzheimer's disease. Alzheimers Res Ther 2015;7:67.
[12] Tan SB, Machin D. Phase II clinical trials. In: Gad CS, ed. Clinical Trials Handbook. New York, New York: John Wiley & Sons, Inc.; 2009. p. 255–77.
[13] Wang SJ, Hung HM, O'Neill R. Adaptive design clinical trials and trial logistics models in CNS drug development. Eur Neuropsychopharmacol 2011;21:159–66.
[14] Cummings JL. Biomarkers in Alzheimer's disease drug development. Alzheimers Dement 2011;7:e13–44.
[15] Cummings JL, Zhong K. Repackaging FDA-approved drugs for degenerative diseases: promises and challenges. Expert Rev Clin Pharmacol 2014;7:161–5.
[16] Mattsson N, Carrillo MC, Dean RA, Devous MD Sr, Nikolcheva T, Pesini P, et al. Revolutionizing Alzheimer's disease and clinical trials through biomarkers. Alzheimers Dement (Amst) 2015;1:412–9.
[17] Sperling RA, Jack CR Jr, Black SE, Frosch MP, Greenberg SM, Hyman BT, et al. Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: recommendations from the Alzheimer's Association Research Roundtable Workgroup. Alzheimers Dement 2011;7:367–85.
[18] Viglietta V, O'Gorman J, Williams L, Chen T, Enayetallah A, Chiao P, et al. Titration dosing of aducanumab: results of a 12-month interim analysis from a randomized, double-blind, placebo-controlled phase 1b study (PRIME) in patients with prodromal or mild Alzheimer's disease (S7.003). Neurology 2017;88(S7.003):16.
[19] Appleby BS, Cummings JL. Discovering new treatments for Alzheimer's disease by repurposing approved medications. Curr Top Med Chem 2013;13:2306–27.
[20] 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.
[21] Jekunen A. Decision-making in product portfolios of pharmaceutical research and development–managing streams of innovation in highly regulated markets. Drug Des Devel Ther 2014;8:2009–16.
[22] Gauthier S, Feldman HH, Schneider LS, Wilcock GK, Frisoni GB, Hardlund JH, et al. Efficacy and safety of tau-aggregation inhibitor therapy in patients with mild or moderate Alzheimer's disease: a randomised, controlled, double-blind, parallel-arm, phase 3 trial. Lancet 2016;388:2873–84.
[23] Zarin DA, Ide NC, Tse T, Harlan WR, West JC, Lindberg DA. Issues in the registration of clinical trials. JAMA 2007;297:2112–20.
[24] De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. N Engl J Med 2004;351:1250–1.
[25] Babic T, Riordan HJ. Improving screen fail and recruitment rates in Alzheimer's disease clinical trials. J Clin Stud 2016;8:38–40.
[26] Cummings J, Reynders R, Zhong K. Globalization of Alzheimer's disease clinical trials. Alzheimers Res Ther 2011;3:24.
[27] Cummings JL, Aisen P, Barton R, Bork J, Doody R, Dwyer J, et al. Re-engineering Alzheimer clinical trials: Global Alzheimer Platform Network. J Prev Alzheimers Dis 2016;3:114–20.
[28] Weiner MW, Veitch DP, Aisen PS, Beckett LA, Cairns NJ, Green RC, et al. The Alzheimer's Disease Neuroimaging Initiative 3: continued innovation for clinical trial improvement. Alzheimers Dement 2017;13:561–71.
[29] Menting KW, Claassen JA. Beta-secretase inhibitor; a promising novel therapeutic drug in Alzheimer's disease. Frontiers in Aging Neuroscience 2014;6:165.
[30] Hamada Y, Kiso Y. New directions for protease inhibitors directed drug discovery. Biopolymers 2016;106:563–79.
[31] Evin G. Future therapeutics in Alzheimer's disease: development status of BACE inhibitors. BioDrugs 2016;30:173–94.
[32] Vassar R, Kuhn PH, Haass C, Kennedy ME, Rajendran L, Wong PC, et al. Function, therapeutic potential and cell biology of BACE

proteases: current status and future prospects. J Neurochem 2014; 130:4–28.
[33] Hawkes N. Merck ends trial of potential Alzheimer's drug verubecestat. BMJ 2017;356: j845.
[34] Le Couteur DG, Hunter S, Brayne C. Solanezumab and the amyloid hypothesis for Alzheimer's disease. BMJ 2016;355: i6771.
[35] Sevigny J, Chiao P, Bussière T, Weinreb PH, Williams L, Maier M, et al. The antibody aducanumab reduces Abeta plaques in Alzheimer's disease. Nature 2016;537:50–6.
[36] Snyder HM, Hendrix J, Bain LJ, Carrillo MC. Alzheimer's disease research in the context of the national plan to address Alzheimer's disease. Mol Aspects Med 2015;43-44:16–24.
[37] Scott TJ, O'Connor AC, Link AN, Beaulieu TJ. Economic analysis of opportunities to accelerate Alzheimer's disease research and development. Ann N Y Acad Sci 2014;1313:17–34.
[38] Cummings JL, Morstorf T, Zhong K. Alzheimer's disease drug-development pipeline: few candidates, frequent failures. Alzheimers Res Ther 2014;6:37.
[39] 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.
[40] Refolo LM, Fillit HM. Partnerships between philanthropy, government and industry are needed to advance drug discovery for neurodegenerative diseases. Curr Alzheimer Res 2006;3:175–6.
[41] Fernandez JM, Stein RM, Lo AW. Commercializing biomedical research through securitization techniques. Nat Biotechnol 2012; 30:964–75.
[42] Lo AW, Ho C, Cummings J, Kosik KS. Parallel discovery of Alzheimer's therapeutics. Sci Transl Med 2014;6:241cm5.