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Featured Article

Alzheimer's disease drug development pipeline: 2018

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Abstract

Introduction: Treatments for Alzheimer's disease (AD) are needed due to the growing number of individuals with preclinical, prodromal, and dementia forms of AD. Drug development for AD therapies can be examined by inspecting the drug development pipeline as represented on clinicaltrials.gov.

Methods: Clinicaltrials.gov was assessed as of January 30, 2018 to determine AD therapies represented in phase I, phase II, and phase III.

Results: There are 112 agents in the current AD treatment pipeline. There are 26 agents in 35 trials in phase III, 63 agents in 75 trials in phase II, and 23 agents in 25 trials in phase I. A review of the mechanisms of actions of the agents in the pipeline shows that 63% are disease-modifying therapies, 22% are symptomatic cognitive enhancers, and 12% are symptomatic agents addressing neuropsychiatric and behavioral changes. Trials in phase III are larger and longer than phase II or phase I trials, particularly those involving disease-modifying agents. Comparison with the 2017 pipeline shows that there are four new agents in phase III, 14 in phase II, and eight in phase I. Inspection of the use of biomarkers as revealed on clinicaltrials.gov shows that amyloid biomarkers are used as entry criterion in 14 phase III disease-modifying agent trials and 17 disease-modifying agent trials in phase II. Twenty-one trials of disease-modifying agents in phase II did not require biomarker confirmation for AD at trial entry.

Discussion: The AD drug development pipeline is slightly larger in 2018 than in 2017. Trials increasingly include preclinical and prodromal populations. There is an increase in nonamyloid mechanisms of action for drugs in earlier phases of drug development. Biomarkers are increasingly used in AD drug development but are not used uniformly for AD diagnosis confirmation.

Keywords: Alzheimer's; Pipeline; Clinicaltrials.gov; Biomarkers; Drug development; Clinical trials; Monoclonal antibodies; Amyloid; Tau; Alzheimer's disease drug development pipeline: 2018

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder with cognitive, functional, and behavioral alterations [1,2]. AD is age related and is becoming markedly more common with the aging of the world's population. It is estimated that by 2050, one in every 85 people will be living with AD [3]. Nearly eightfold as many people have preclinical AD as have symptomatic AD and are at risk for progressing to manifest disease [4]. Disease-modifying therapies (DMTs) that will prevent or delay the onset or slow the progression of AD are urgently needed. A modest 1-year delay in onset by 2020 would result in there being 9.2 million fewer cases in 2050 [3]. Similarly, medications to effectively improve cognition or ameliorate neuropsychiatric symptoms of patients in the symptomatic phases of AD are needed to improve memory and behavior [5].

In this update of our annual review of the AD drug development pipeline, we provide a summary of the current state of progress in developing new therapies for AD [6,7]. We discuss each phase of the AD pipeline (I, II, and III) and

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describe DMTs, cognitive-enhancing agents, and treatments for behavioral disturbances in AD that are in development. We note the use of biomarkers in clinical trials. We describe evolving targets of the agents in the pipeline. We discuss trial infrastructure changes that may accelerate clinical trials and drug development. Our goal is to provide insight into the drug development process and to help drug developers and clinical trialists learn from the current pipeline experience.

2. Methods

This annual review is based on clinical trial activity as recorded in clinicaltrials.gov, a comprehensive US government database. The US law requires that all clinical trials conducted in the United States be registered on the site. The "common rule" governing clinicaltrials.gov was recently updated and mandated registration of all trials from sponsors with an Investigational New Drug or Investigational New Device [8,9]. Trials must be registered within 21 days of the enrollment of the first trial participant. Results for the primary outcome measures must be submitted to clincaltrials.gov within 12 months of completion of final data collection. Compliance with trial registration is high [10–12]; compliance with results reporting is lower [13]. Clinicaltrials.gov can be regarded as a comprehensive and valid data source for the study of clinical trials conducted in the United States. Not all non-US trials are registered on clinicaltrials.gov—especially phase I trials—and our findings may underrepresent the agents populating global phase I efforts.

Results reported here are based on trials registered on clinicaltrials.gov as of January 30, 2018. We include all trials of all agents in phase I, II, and III; some trials are presented as I/II or II/III in the database, and we use that nomenclature in the review. In our trial database, we entered the trial title; beginning date; projected end date; calculated duration; planned enrollment number; number of arms of the study (usually a placebo arm and one or more treatment arms with different doses); whether a biomarker was described; subject characteristics; and sponsorship by a biopharma company, National Institutes of Health, academic medical center, "other" entity such as a consortium or a philanthropic organization, or a combination of these sponsors. Using the clinicaltrials.gov classification, we included trials that were recruiting, active but not recruiting (e.g., trials that have completed recruiting and are continuing with the exposure portion of the trial), enrolling by invitation, and not yet recruiting. We did not include trials listed as completed, terminated, suspended, unknown, or withdrawn because information on these trials is often incomplete. We included all pharmacologic trials listed in the database; we did not include trials of nonpharmacologic therapeutic approaches such as devices, cognitive therapies, caregiver interventions, supplements, and medical foods. We did not include trials of biomarkers although we noted whether biomarkers were used in the trials of interest.

Drug targets and mechanism of action (MOA) of treatments are important aspects of this review. MOA was determined from the information on clinicaltrials.gov or from a comprehensive search of the literature. In a few cases, the mechanism is undisclosed and could not be identified in the literature, and we note these agents as having an "unknown" MOA. 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 targeting amyloid-related mechanisms, those that have tau-related MOAs, and those with "other" mechanisms such as neuroprotective agents, anti-inflammatory drugs, growth factors, or agents with metabolic effects. Stem cell therapies were included in the "other" category. Some agents have multiple effects and might be expected to have symptomatic and disease-modifying properties. We classified these drugs as symptomatic or DMTs based on the trial design. Agents in large, long (12–24 months) trials with biomarker outcomes are listed as DMTs. Those in smaller, shorter (3–6 months) trials with cognitive or behavioral outcomes and no biomarkers are listed as symptomatic. Agents could change classification as more information accrues.

3. Results

3.1. Overview

Fig. 1 provides an overview of all agents identified in the current AD pipeline. The main circles of the figure reveal the stage 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, cognitively normal at-risk individuals, prodromal AD, and AD dementia).

In total, there are 112 agents in the pipeline as shown on clinicaltrials.gov. We identified 26 agents in 35 trials in phase III, 63 agents in 75 trials in phase II, and 23 agents in 25 trials in phase I. Review of the MOAs of pipeline agents showed that 63% are DMTs, 22% are symptomatic cognitive enhancers, 12% are symptomatic agents addressing neuropsychiatric and behavioral changes, and 3% have undisclosed MOAs.

3.2. Phase III

Phase III of the 2018 AD pipeline has 26 agents; 17 DMTs, one cognitive-enhancing agent, and eight drugs for behavioral symptoms (Fig. 1, Table 1). Among the DMTs, 14 addressed amyloid targets, one involved a tau-related target, one involved neuroprotection, and one had a metabolic MOA. The DMTs include six immunotherapies (all addressing amyloid). Of the DMTs, two are repurposed agents approved for use in another indication (insulin, albumin plus immunoglobulin). Of the drugs with amyloid targets, there were five Beta-site Amyloid precursor protein Cleavage

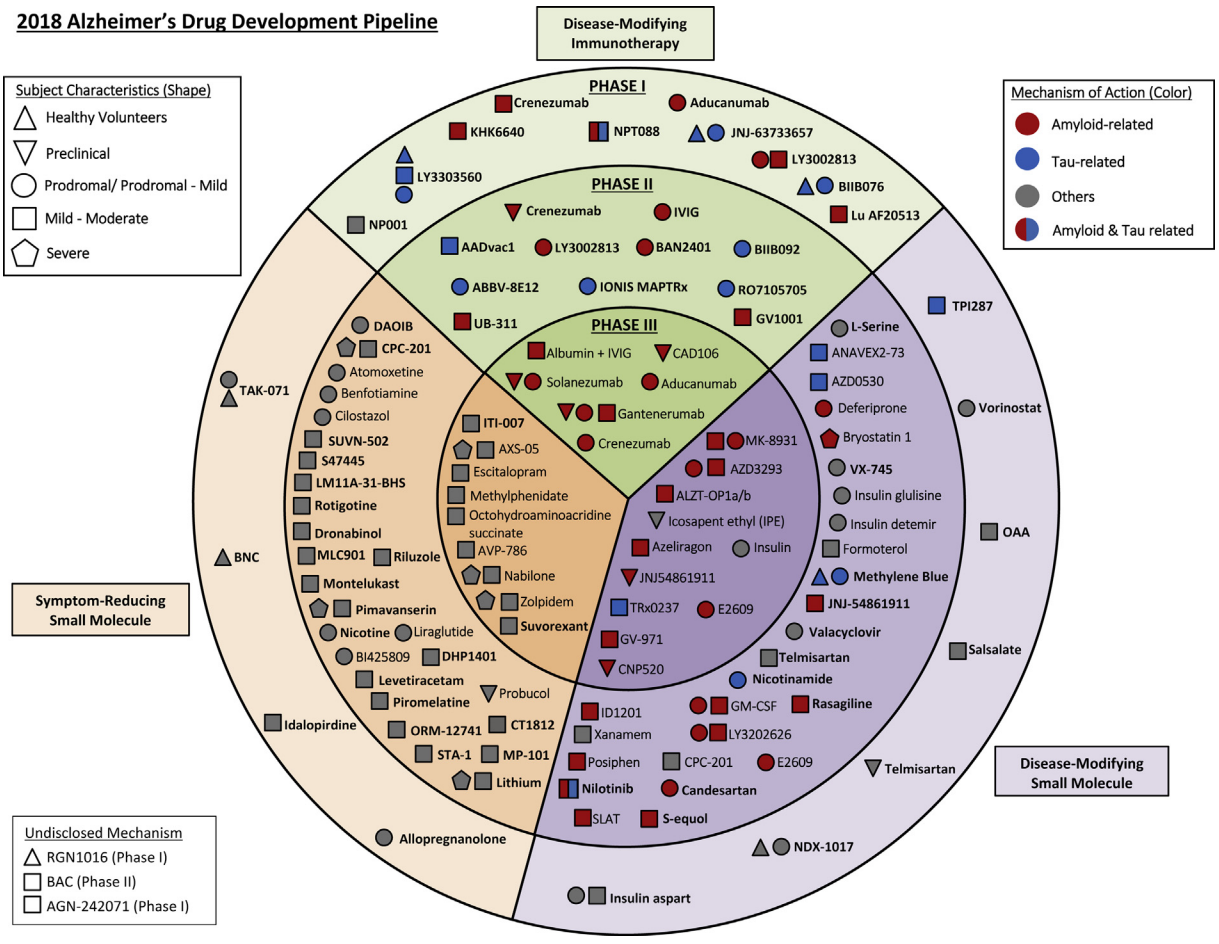

Fig. 1. Agents in clinical trials for treatment of Alzheimer's disease in 2018 (from clinicaltrials.gov accessed January 30, 2018).

Enzyme inhibitors, six immunotherapies, and three antiaggregation agents. Fig. 2 shows the MOAs of agents in phase III.

There is a movement toward treating patients with milder forms of AD including cognitively normal individuals with evidence of amyloid pathology (by cerebrospinal fluid [CSF] measures or amyloid positron emission tomography [PET]) or who have genetic profiles that place them at high risk for developing AD (Table 2). In phase III, there were six prevention trials enrolling cognitively normal participants. There were 12 trials of patients with prodromal AD/mild cognitive impairment (MCI) or prodromal/mild AD; 14 trials of patients with mild-moderate AD; and three trials of patients with mild-moderate/severe AD.

Phase III trials involved a mean of 860 participants and had a mean duration of 1841 days or 263 weeks (including the recruitment and the treatment period). DMT trials were longer than trials of agents with other MOAs (2139 days or 306 weeks; 121 treatment weeks) and larger—including an average of 1066 participants. The mean duration of cognitive enhancer trials was 914 days or 131 weeks (26 treatment weeks), and they included an average of 600 participants. Trials of drugs for behavioral symptoms average 1119 days or 160 weeks (15 treatment weeks) and included a mean of 314 patients. For DMTs, the average duration of treatment exposure is 121 weeks; the mean period from trial initiation to primary completion date (final data collection date for primary outcome measure) is 239 weeks. This indicates that 118 weeks—nearly equal to the treatment period—is the average anticipated recruitment time. When examined by trial population, prevention trials are 420 weeks in duration; trials for patients with MCI/prodromal/prodromal-mild AD are 289 weeks in duration; and trials for patients mild-moderate AD are 235 weeks in duration. Planned recruitment periods for these three types of trials are 164, 161, and 116 weeks, respectively.

3.3. Phase II

In 2018, there are 75 trials involving 63 agents in phase II of the AD pipeline (Table 3). Sixteen trials involved patients with prodromal or prodromal and mild AD, 28 were trials for mild-moderate AD, one included patients with MCI and mild-moderate AD, one was a prevention trial, one included patients with MCI or healthy volunteers, and one trial was for severe AD. Of the symptomatic agent trials, one was

Table 1
Agents currently in phase III of Alzheimer's disease drug development (as of January 30, 2018)

Agent	Agent mechanism class	Mechanism of action	Therapeutic purpose	Clinicaltrials.gov ID	Status	Sponsor	Start date	Estimated end date
Aducanumab	Anti-amyloid	Monoclonal antibody	Remove amyloid (DMT)	NCT02484547	Recruiting	Biogen	September-15	April-22
				NCT02477800	Recruiting	Biogen	August-15	March-22
Albumin + immunoglobulin	Anti-amyloid	Polyclonal antibody	Remove amyloid (DMT)	NCT01561053*	Active, not recruiting	Grifols	March-12	December-17
ALZT-OP1a + ALZT-OP1b (cromolyn + ibuprofen)	Anti-amyloid, anti-inflammatory	Mast cell stabilizer (cromolyn), anti-inflammatory (ibuprofen)	Reduce neuronal damage; mast cells may also play a role in amyloid pathology (DMT)	NCT02547818	Recruiting	AZTherapies, Pharma Consulting Group, KCAS Bio, APCER Life Sciences	September-15	November-19
AVP-786	Neurotransmitter based	Sigma 1 receptor agonist; NMDA receptor antagonist	Improve neuropsychiatric symptoms (agitation)	NCT02442765	Recruiting	Avanir	September-15	July-18
				NCT02446132	Recruiting-EXT	Avanir	December-15	March-21
AZD3293 (LY3314814)	Anti-amyloid	BACE1 inhibitor	Reduce amyloid production (DMT)	NCT02245737*	Active, not recruiting	AstraZeneca, Eli Lilly	September-14	September-19
				NCT02783573	Recruiting	AstraZeneca, Eli Lilly	July-16	March-21
				NCT02972658	Recruiting-EXT	AstraZeneca, Eli Lilly	March-17	September-20
AXS-05	Neurotransmitter based	Sigma 1 receptor agonist; NMDA receptor antagonist (dextromethorphan); serotonin norepinephrine reuptake inhibition (bupropion)	Improve neuropsychiatric symptoms (agitation)	**NCT03226522**	Recruiting	Axsome Therapeutics	July-17	September-19
CAD106 & CNP520	Anti-amyloid	Amyloid vaccine, BACE inhibitor	Remove/reduce amyloid (DMT)	NCT02565511*	Recruiting	Novartis, Amgen, NIA, Alzheimer's Association, Banner Alzheimer's Institute	November-15	May-24
CNP520	Anti-amyloid	BACE Inhibitor	Reduce amyloid production (DMT)	**NCT03131453**	Recruiting	Novartis, Amgen, Banner Alzheimer's Institute	August-17	July-24
Crenezumab	Anti-amyloid	Monoclonal antibody	Remove amyloid (DMT)	NCT02670083	Active, not recruiting	Roche/Genentech	March-16	July-21
				NCT03114657	Recruiting	Roche/Genentech	March-17	October-22
E2609 (elenbecestat)	Anti-amyloid	BACE inhibitor	Reduce amyloid production (DMT)	NCT02956486	Recruiting	Eisai, Biogen	October-16	December-20
				NCT03036280	Recruiting	Eisai, Biogen	December-16	December-20
Escitalopram	Neurotransmitter based	Serotonin reuptake inhibition	Improve neuropsychiatric symptoms (agitation)	**NCT03108846**	Not yet recruiting	NIA, JHSPH Center for Clinical Trials	September-17	March-21

(*Continued*)

Table 1
Agents currently in phase III of Alzheimer's disease drug development (as of January 30, 2018) (*Continued*)

Agent	Agent mechanism class	Mechanism of action	Therapeutic purpose	Clinicaltrials.gov ID	Status	Sponsor	Start date	Estimated end date
Gantenerumab	Anti-amyloid	Monoclonal antibody	Remove amyloid (DMT)	NCT02051608	Active, not recruiting	Roche	March-14	November-19
				NCT01224106	Active, not recruiting	Roche	November-10	July-20
Gantenerumab and solanezumab and JNJ-54861911	Anti-amyloid	Monoclonal antibody, BACE inhibitor	Remove amyloid/reduce amyloid production (DMT)	NCT01760005*	Recruiting	Washington University, Eli Lilly, Roche, NIA, Alzheimer's Association	December-12	December-23
Icosapent ethyl (IPE)	Neuroprotective	Purified form of the omega-3 fatty acid EPA	Protect neurons from disease pathology	NCT02719327*	Recruiting	VA Office of Research and Development, University of Wisconsin, Madison	December-16	November-21
Insulin intranasal (Humulin)	Metabolic	Replace insulin in the brain	Enhance cell signaling and neurogenesis (cognitive enhancer)	NCT01767909*	Active, not recruiting	University of Southern California, NIA, ATRI, Wake Forest University	January-14	December-18
ITI-007	Neurotransmitter based	5-HT2A antagonist, dopamine receptor modulator	Improve neuropsychiatric symptoms (agitation)	NCT02817906	Recruiting	Intra-Cellular Therapies, Inc.	June-16	August-18
JNJ-54861911	Anti-amyloid	BACE inhibitor	Reduce amyloid production (DMT)	NCT02569398*	Recruiting	Janssen	November-15	April-24
Methylphenidate	Neurotransmitter based	Dopamine reuptake inhibitor	Improve neuropsychiatric symptoms (apathy)	NCT02346201	Recruiting	Johns Hopkins, NIA	January-16	August-20
MK-8931 (verubecestat)	Anti-amyloid	BACE inhibitor	Reduce amyloid production (DMT)	NCT01953601	Active, not recruiting	Merck	November-13	March-21
MK-4305 (suvorexant)	Neurotransmitter based	Dual orexin receptor antagonist	Improve neuropsychiatric symptoms (sleep disorders)	NCT02750306	Recruiting	Merck	May-16	April-18
Nabilone	Neurotransmitter based	Cannabinoid (receptor agent)	Improve neuropsychiatric symptoms (agitation)	NCT02351882*	Recruiting	Sunnybrook Health Sciences Centre	January-15	January-18
Octohydroaminoacridine succinate	Neurotransmitter based	Acetylcholinesterase inhibitor	Improve acetylcholine signaling (cognitive enhancer)	**NCT03283059**	Recruiting	Shanghai Mental Health Center, Changchun-Huayang High-tech Co., Jiangsu Sheneryang High-tech Co.	August-17	February-20

(*Continued*)

Table 1
Agents currently in phase III of Alzheimer's disease drug development (as of January 30, 2018) (*Continued*)

Agent	Agent mechanism class	Mechanism of action	Therapeutic purpose	Clinicaltrials.gov ID	Status	Sponsor	Start date	Estimated end date
GV-971 (Sodium Oligo-mannurarate)	Anti-amyloid	Inhibit amyloid aggregation	Remove amyloid plaque load (DMT)	NCT02293915	Recruiting	Shanghai Green valley Pharmaceutical	April-14	September-18
Solanezumab	Anti-amyloid	Monoclonal antibody	Remove amyloid (DMT)	NCT02008357	Active, not recruiting	Eli Lilly, ATRI	February-14	July-22
TRx0237 (LMTX)	Anti-tau	Tau protein aggregation inhibitor	Reduce tau-mediated neuronal damager (DMT)	NCT02245568	Recruiting, Extension	TauRx Therapeutics	August-14	September-17
TTP488 (azeliragon)	Anti-amyloid, anti-inflammatory	RAGE antagonist	Reduce amyloid uptake in brain and lower inflammation in glial cells (DMT/cognitive enhancer)	NCT02080364 NCT02916056	Active, not recruiting Recruiting – EXT	vTv Therapeutics	April-15 December-16	January-19 November-20
Zolpidem	Neurotransmitter based	Positive allosteric modulator of GABA-A receptors	Improve neuropsychiatric symptoms (sleep disorders)	**NCT03075241**	Recruiting	Brasilia University Hospital	October-16	December-18

Abbreviations: ATRI, Alzheimer's Therapeutic Research Institute; BACE, Beta-site Amyloid precursor protein Cleaving Enzyme; DMT, disease-modifying therapy; EPA, eicosapentaenoic acid; GABA, gamma-aminobutyric acid; NIA, National Institute on Aging; RAGE, receptor for advanced glycation end products.

NOTE. Twenty-six agents in 35 phase III clinical trials currently ongoing as of January 30, 2018 according to clinicaltrials.gov.

NOTE. Bolded terms represent new entries into the 2018 phase III pipeline.

*Phase II/III trials.

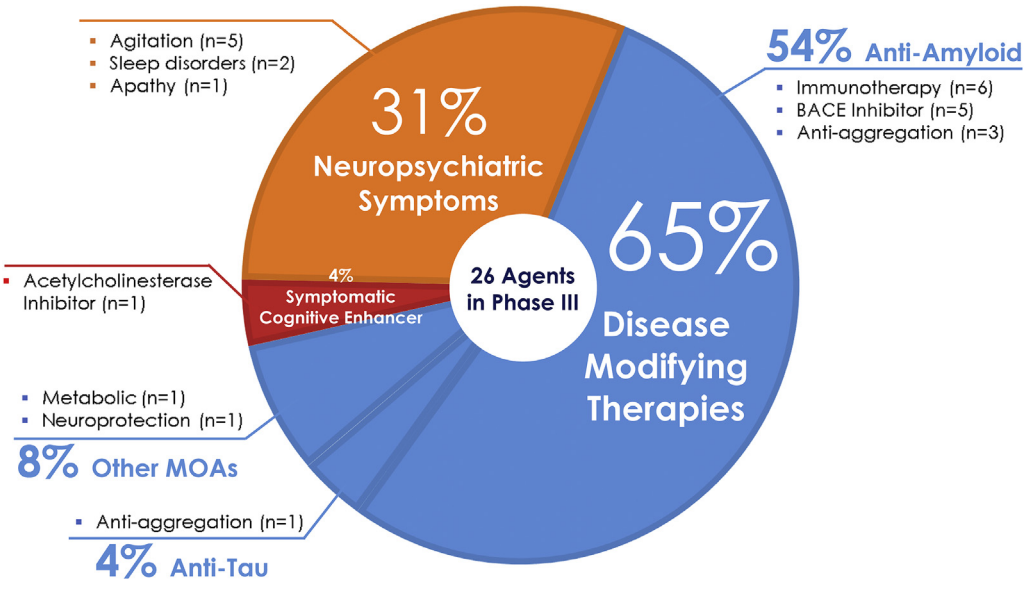

Fig. 2. Mechanisms of action of agents in phase III.

for preclinical AD, seven were for prodromal mild AD, 16 were for mild-moderate AD, and three were for mild-moderate or severe AD.

Of the 63 agents, there were 36 DMTs, 21 cognitive-enhancing agents, five drugs for behavioral symptoms, and one agent with an unknown MOA (Fig. 1; Table 3). Among the DMTs, 18 involved amyloid targets, nine addressed tau-related targets, one had a mechanism relevant to both amyloid- and tau-related targets, and eight had other MOAs (e.g., neuroprotection, metabolic, or anti-inflammatory). The DMTs include 11 immunotherapies (six addressing amyloid and five addressing tau). Of the DMTs, 12 are repurposed agents approved for use in another indication. There are eight trials involving stem cell therapies.

Of the drugs with amyloid targets, there were three Beta-site Amyloid percursor protein Cleavage Enzyme inhibitors, six immunotherapies, and two antiaggregation agents. Four agents involved antiaggregation and neuroprotection, and three agents were antiaggregation, neuroprotective, and metabolic agents. Fig. 3 shows the MOAs of agents in phase II.

Phase II trials are shorter in duration and smaller in terms of participant number than phase III trials: Phase II trials had a mean duration of 1221 days or 174 weeks (recruitment plus exposure period) and included an average of 156 participants in each trial. The average treatment period is 39 weeks.

3.4. Phase I

Phase I first-in-human trials are generally conducted in healthy volunteers and sometimes include a cohort of healthy elderly to begin to assess whether age affects the metabolism or excretion of the test agent. In some cases, phase I/IIa trials assess preliminary efficacy in patients

Table 2
Prevention trial by phase

Phase	Agent	Trial	Sponsor	Means of defining risk for AD dementia
III	Solanezumab	A4	Eli Lilly	Amyloid PET
II/III	CAD106, CNP520	Generation S1	Novartis	Homozygous APOE4
II/III	CNP520	Generation S2	Novartis	Amyloid PET or CSF
II/III	Icosapent ethyl (IPE)	BRAVE-EPA	VA Office of Research and Development	Parental history of AD and increased prevalence of APOE4 allele
II/III	JNJ-54861911	Early	Janssen	Amyloid PET or CSF
II/III	Gantenerumab, solanezumab, JNJ-54861911	DIAN-TU	Eli Lilly, Roche, Janssen, NIA	Family history of autosomal dominant AD
II	Crenezumab	GN28352	Genentech	Presenilin-1 E280 A mutation
I/II	Probucol	DEPEND	Douglas Mental Health University	Family history of AD
I	Telmisartan	HEART	Emory University	Parental history of AD

Abbreviations: AD, Alzheimer's disease; APOE, apolipoprotein E; BRAVE-EPA, Brain Amyloid and Vascular Effects of Eicosapontaenoic Acid; DEPEND, Dosage and Etiology of Protocols Induced apoE to Negate Cognitive Deterioration; DIAN-TU, Dominantly Inherited Alzheimer Network-Treatment Unit; HEART, Health Evaluation of African Americans Using RAS Therapy; NIA, National Institute on Aging; PET, positron emission tomography.

Table 3
Agents currently in phase II of Alzheimer's disease drug development (as of January 30, 2018)

Agent	Agent mechanism class	Mechanism of action	Therapeutic purpose	Clinicaltrials.gov ID	Status	Sponsor	Start date	Estimated end date
AADvac1	Anti-tau	Active immunotherapy	Remove tau (DMT)	NCT02579252	Active, not recruiting	Axon Neuroscience	March-16	June-19
ABBV-8E12	Anti-tau	Monoclonal antibody	Remove tau (DMT)	NCT02880956	Recruiting	AbbVie	October-16	June-21
ANAVEX 2-73	Anti-tau, metabolic	Sigma-1 receptor agonist (high affinity); muscarinic agonist (low affinity); GSK-3β inhibitor	Improve cell signaling (cognitive enhancer) and reduce tau phosphorylation (DMT)	NCT02244541	Active, not recruiting	Anavex Life Sciences	December-14	October-16
				NCT02756858	Recruiting, extension	Anavex Life Sciences	March-16	November-18
AstroStem	Regenerative	Autologous adipose tissue derived mesenchymal stem cells	Regenerate neurons	**NCT03117738**	Recruiting	Nature Cell Co.	April-17	November-18
Atomoxetine	Neurotransmitter based	Norepinephrine reuptake inhibitor	Improve neurotransmission (cognitive enhancer) and improve behavioral symptoms	NCT01522404	Active, not recruiting	Emory University, NIA	March-12	June-18
AZD0530 (saracatinib)	Metabolic, anti-tau	Tyrosine kinase Fyn inhibitor	Improve synaptic dysfunction (cognitive enhancer), reduce tau phosphorylation (DMT)	NCT02167256	Active, not recruiting	Yale University, ATRI, AstraZeneca	December-14	December-17
BAC	Undisclosed	Undisclosed mechanism	Undisclosed	NCT02886494	Recruiting	Charsire Biotechnology	December-16	November-19
				NCT02467413	Not yet recruiting	Charsire Biotechnology, A2 Healthcare Taiwan Corporation	December-17	December-17
BAN2401	Anti-amyloid	Monoclonal antibody	Remove amyloid (DMT)	NCT01767311	Active, not recruiting	Eisai	December-12	November-18
Benfotiamine	Metabolic	Synthetic thiamine (B1)	Improve multiple cellular processes (cognitive enhancer)	NCT02292238	Recruiting	Burke Medical Research Institute, Columbia University, NIA, ADDF	November-14	November-19
BI 425809	Neurotransmitter based	Glycine transporter 1 inhibitor	Facilitate NMDA receptor activity (cognitive enhancer)	NCT02788513	Recruiting	Boehringer Ingelheim	August-16	September-20
BIIB092	Anti-tau	Monoclonal antibody	Remove tau (DMT)	**NCT03352557**	Not yet recruiting	Biogen	February-18	September-20
Bryostatin 1	Metabolic, anti-amyloid	Protein kinase C modulator	Improve cellular processes (cognitive enhancer) and reduce amyloid pathology (DMT)	NCT02431468	Active, not recruiting	Neurotrope Bioscience	November-15	May-17
Candesartan	Neuroprotective, metabolic, anti-amyloid	Angiotensin receptor blocker	Improve vascular functioning and effects on amyloid pathology (DMT)	NCT02646982	Recruiting	Emory University	June-16	September-21

(*Continued*)

Table 3
Agents currently in phase II of Alzheimer's disease drug development (as of January 30, 2018) (*Continued*)

Agent	Agent mechanism class	Mechanism of action	Therapeutic purpose	Clinicaltrials.gov ID	Status	Sponsor	Start date	Estimated end date
CB-AC-02 (Placenta derived-MSCs)	Regenerative	Stem cell therapy	Regenerate neurons	NCT02899091*	Not yet recruiting	CHA Biotech Co.	September-16	June-18
Cilostazol	Neuroprotective, metabolic	Phosphodiesterase 3 antagonist	Regulate cAMP and improve synaptic function (cognitive enhancer)	NCT02491268	Recruiting	National Cerebral and Cardiovascular Center, Japan	July-15	December-20
CPC-201 (donepezil/ solifenacin combination)	Neurotransmitter based	Cholinesterase inhibitor + peripheral cholinergic antagonist	Improve acetylcholine signaling (cognitive enhancer)	NCT02549196	Active, not recruiting	Allergan	October-15	September-17
Crenezumab	Anti-amyloid	Monoclonal antibody	Remove amyloid (DMT)	NCT01998841	Active, not recruiting	Genentech, NIA Banner Alzheimer's Institute	December-13	February-22
CT1812	Metabolic	Sigma-2 receptor modulator	Improve synaptic dysfunction (cognitive enhancer)	NCT02907567*	Recruiting	Cognition Therapeutics	September-16	May-17
DAOIB	Neurotransmitter based	NMDA receptor modulation	Enhance NMDA activity (cognitive enhancer)	NCT02239003	Recruiting	Chang Gung Memorial Hospital, Taiwan	January-12	December-17
Deferiprone	Neuroprotective, anti-amyloid	Iron chelating agent	Reduce reactive oxygen species that damage neurons; effect on amyloid and BACE pathology (DMT)	**NCT03234686**	Recruiting	Neuroscience Trials Australia	January-18	December-21
DHP1401	Neuroprotective, metabolic	Affects cAMP activity	Improve synaptic function (cognitive enhancer)	**NCT03055741**	Recruiting	Daehwa Pharmaceutical Co.	December-16	September-18
Dronabinol	Neurotransmitter based	CB1 and CB2 endocannabinoid receptor partial agonist	Improve neuropsychiatric symptoms (agitation)	NCT02792257	Recruiting	Mclean Hospital, Johns Hopkins University	March-17	December-20
E2609	Anti-amyloid	BACE inhibitor	Reduce amyloid production (DMT)	NCT02322021	Active, not recruiting	Eisai, Biogen	November-14	April-18
Formoterol	Metabolic	β2 adrenergic receptor agonist	Effects on multiple cellular pathways (DMT)	NCT02500784	Recruiting	Palo Alto Veterans Institute for Research, Mylan, Alzheimer's Association	January-15	July-18
GV1001	Metabolic, anti-amyloid	Telomerase reverse transcriptase peptide vaccine	Effects on multiple cellular pathways including amyloid pathology (DMT)	**NCT03184467**	Recruiting	GemVax & Kael	June-17	June-19

(*Continued*)

Table 3
Agents currently in phase II of Alzheimer's disease drug development (as of January 30, 2018) (*Continued*)

Agent	Agent mechanism class	Mechanism of action	Therapeutic purpose	Clinicaltrials.gov ID	Status	Sponsor	Start date	Estimated end date
hUCB-MSCs	Regenerative	Stem cell therapy	Regenerate neurons	NCT02054208*	Recruiting	Medipost Co.	February-14	July-19
				NCT01547689*	Active, not recruiting	Affiliated Hospital to Academy of Military Medical Sciences, China	March-12	December-16
				NCT02513706	Not yet recruiting	South China Research Center	May-16	October-19
				NCT02672306*	Not yet recruiting	South China Research Center	May-16	October-19
				NCT02833792	Recruiting	Stemedica Cell Technologies	June-16	June-18
				NCT03172117	Recruiting	Medipost Co.	May-17	December-21
ID1201	Anti-amyloid, metabolic, neuroprotective	Phosphatidylinositol 3-kinase/Akt pathway activation	Effects on multiple cellular pathways including amyloid metabolism (DMT)	**NCT03363269**	Recruiting	IlDong Pharmaceutical Co	April-16	December-18
Insulin detemir (intranasal)	Metabolic	Increases insulin signaling in the brain	Enhance cell signaling and growth (DMT)	NCT01595646	Active, not recruiting	Wake Forest School of Medicine, Alzheimer's Association	November-11	March-17
Insulin glulisine (intranasal)	Metabolic	Increases insulin signaling in the brain	Enhance cell signaling and growth (DMT)	NCT02503501	Recruiting	Health Partners Institute	August-15	September-18
IONIS MAPTRx	Anti-tau	Microtubule-associated tau (MAPT) RNA inhibitor; antisense oligonucleotides	Reduce tau production (DMT)	**NCT03186989**	Recruiting	Ionis Pharmaceuticals, Biogen	June-17	February-20
JNJ-54861911	Anti-amyloid	BACE inhibitor	Reduce amyloid production (DMT)	NCT02406027	Active, not recruiting, Extension	Janssen	July-15	October-22
Levetiracetam	Metabolic	Anticonvulsant	Reduce neuronal hyperactivity (cognitive enhancer)	NCT02002819	Recruiting	University of California, San Francisco	June-14	December-17
Liraglutide	Metabolic, neuroprotective	Glucagon-like peptide 1 receptor agonist	Enhance cell signaling (cognitive enhancer)	NCT01843075	Recruiting	Imperial College London	January-14	March-19
Lithium	Neurotransmitter based	Ion channel modulator	Improve neuropsychiatric symptoms (agitation, mania, psychosis)	NCT02129348	Recruiting	New York State Psychiatric Institute, NIA	June-14	April-19
LM11A-31-BHS	Neuroprotective	Targets the p75 neurotrophin receptor	Improve synaptic functioning (cognitive enhancer)	**NCT03069014**	Recruiting	PharmatrophiX Inc., NIA	February-17	October-19
L-Serine	Neuroprotective	Amino acid	Stabilize protein misfolding (DMT)	**NCT03062449**	Recruiting	Dartmouth-Hitchcock Medical Center, Brain Chemistry Laboratories	March-17	August-18

(*Continued*)

Table 3
Agents currently in phase II of Alzheimer's disease drug development (as of January 30, 2018) (*Continued*)

Agent	Agent mechanism class	Mechanism of action	Therapeutic purpose	Clinicaltrials.gov ID	Status	Sponsor	Start date	Estimated end date
LY3002813	Anti-amyloid	Monoclonal antibody	Remove amyloid (DMT)	**NCT03367403**	Recruiting	Eli Lilly	December-17	December-20
LY3202626	Anti-amyloid	BACE Inhibitor	Reduce amyloid production (DMT)	NCT02791191	Recruiting	Eli Lilly	June-16	June-19
Methylene Blue	Anti-tau	Tau protein aggregation inhibitor	Reduce neurofibrillary tangle formation (DMT)	NCT02380573	Active, not recruiting	Texas Alzheimer's Research and Care Consortium	July-15	July-18
MLC901	Neuroprotective, anti-inflammatory	Natural product consisting of several herbs	Multiple cellular pathways (cognitive enhancer)	**NCT03038035**	Recruiting	National University Hospital, Singapore	December-16	June-19
Montelukast buccal film	Anti-inflammatory	Leukotriene receptor antagonist	Reduce inflammation (cognitive enhancer)	**NCT03402503**	Not yet recruiting	IntelGenx Corp.	February-18	October-19
MP-101	Neuroprotective	Enhances mitochondrial functioning	Improve neuropsychiatric symptoms (psychosis)	**NCT03044249**	Recruiting	Mediti Pharma	May-17	November-18
VX-745 (neflamapimod)	Metabolic	Selective p38 MAPK alpha inhibitor	Affect multiple cellular processes including inflammation and cellular plasticity (DMT)	**NCT03402659**	Recruiting	EIP Pharma, VU University	December-17	July-19
Nicotinamide (Vitamin B3)	Anti-tau, neuroprotective	Histone deacetylase inhibitor	Tau-induced microtubule depolymerization (DMT)	**NCT03061474**	Recruiting	University of California, Irvine	July-17	February-19
Nicotine transdermal	Neurotransmitter based	Nicotinic acetylcholine receptor agonist	Enhance acetylcholine signaling (cognitive enhancer)	NCT02720445	Recruiting	University of Southern California, NIA, ATRI, Vanderbilt University	January-17	December-19
Nilotinib	Anti-tau, anti-amyloid	Tyrosine kinase inhibitor	Reduce amyloid and tau production (DMT)	NCT02947893	Recruiting	Georgetown University	January-17	March-19
Octagam 10%	Anti-amyloid	10% human normal immunoglobulin	Remove amyloid (DMT)	**NCT03319810**	Not yet recruiting	Sutter Health	October-17	October-18
ORM-12741	Neurotransmitter based	Alpha-2c adrenergic receptor antagonist	Improve neuropsychiatric symptoms (agitation)	NCT02471196	Active, not recruiting	Orion Corporation, Janssen	August-15	December-17
Pimavanserin	Neurotransmitter based	5-HT2A inverse agonist	Improve neuropsychiatric symptoms (agitation)	**NCT03118947**	Recruiting	Acadia	February-17	June-20
				NCT02992132	Active, not recruiting	Acadia	November-16	February-18
Piromelatine	Neurotransmitter based	Melatonin receptor agonist; 5-HT 1A and 1D serotonin receptor agonist	Enhance cellular signaling (cognitive enhancer)	NCT02615002	Recruiting	Neurim Pharmaceuticals	November-15	March-18
Posiphen	Anti-amyloid	Selective inhibitor of APP production	Reduce amyloid production (DMT)	NCT02925650*	Recruiting	QR Pharma, ADCS	March-17	December-18
Probucol	Neuroprotective, anti-inflammatory	Non-statin cholesterol reducing agent	Induce APOE activity and improve synaptic functioning (cognitive enhancer)	NCT02707458*	Not yet recruiting	Douglas Mental Health University Institute, Weston Brain Institute, McGill University	April-16	May-18

(*Continued*)

Table 3
Agents currently in phase II of Alzheimer's disease drug development (as of January 30, 2018) (*Continued*)

Agent	Agent mechanism class	Mechanism of action	Therapeutic purpose	Clinicaltrials.gov ID	Status	Sponsor	Start date	Estimated end date
Rasagiline	Neuroprotective, metabolic, anti-amyloid	Monoamine oxidase B inhibitor	Enhance mitochondria activity and inactivate reactive oxygen species (cognitive enhancer), also effect on amyloid pathology (DMT)	NCT02359552	Recruiting	The Cleveland Clinic, Teva	May-15	February-19
Riluzole	Neuroprotective	Glutamate receptor antagonist; glutamate release inhibitor	Inhibit glutamate neurotransmission (cognitive enhancer)	NCT01703117	Recruiting	Rockefeller University	November-13	November-19
RO7105705	Anti-tau	Monoclonal antibody	Remove tau (DMT)	**NCT03289143**	Recruiting	Genentech	October-17	September-22
Rotigotine	Neurotransmitter based	Dopamine agonist	Enhance dopamine neurotransmission (cognitive enhancer)	**NCT03250741**	Recruiting	I.R.C.C.S. Fondazione Santa Lucia	June-16	June-18
S47445	Neurotransmitter based	AMPA receptor agonist	Enhance NMDA receptor activity (cognitive enhancer)	NCT02626572	Active, not recruiting	Servier	February-15	December-17
Sargramostim (GM-CSF)	Anti-amyloid, neuroprotective	Synthetic granulocyte colony stimulator	Stimulate innate immune system to remove amyloid pathology (DMT)	NCT01409915	Active, not recruiting	University of Colorado, Denver, The Dana Foundation	March-11	December-17
S-equol	Neuroprotective, anti-amyloid	Estrogen receptor B agonist	Improve synaptic functioning by competing with amyloid pathology (DMT)	**NCT03101085**	Recruiting	Ausio Pharmaceuticals, University of Kansas	May-17	October-19
Simvastatin + L-Arginine + Tetrahydrobiopterin (SLAT)	Neuroprotective, anti-amyloid	HMG-CoA reductase inhibitor and antioxidant	Reduce cholesterol synthesis thereby reducing amyloid production (DMT)	NCT01439555	Active, not recruiting	University of Massachusetts, Worcester	November-11	December-17
STA-1	Neuroprotective	Antioxidant properties of echinacoside	Reduce oxidative stress (cognitive enhancer)	NCT01255046	Not yet recruiting	Sinphar Pharmaceuticals	December-15	December-18
SUVN-502	Neurotransmitter based	5-HT6 antagonist	Improve neuronal signaling (cognitive enhancer)	NCT02580305	Recruiting	Suven Life Sciences	September-15	September-18
Telmisartan	Neuroprotective, anti-inflammatory	Angiotensin II receptor blocker, PPAR-gamma agonist	Improve vascular functioning (DMT)	NCT02085265	Recruiting	Sunnybrook Health Sciences Centre, ADDF	March-14	March-21
UB-311	Anti-amyloid	Active immunotherapy	Reduce amyloid (DMT)	NCT02551809	Active, not recruiting	United Neuroscience	October-15	December-18
Valacyclovir	Neuroprotective, anti-inflammatory	Antiviral agent	Protect against HSV-1/2 infection and inflammation (DMT)	NCT02997982 **NCT03282916**	Recruiting Not yet recruiting	Umea University New York State Psychiatric Institute, NIH, NIA	December-16 December-17	December-17 August-22

(*Continued*)

Table 3
Agents currently in phase II of Alzheimer's disease drug development (as of January 30, 2018) (*Continued*)

Agent	Agent mechanism class	Mechanism of action	Therapeutic purpose	ClinicalTrials.gov ID	Status	Sponsor	Start date	Estimated end date
Xanamema	Neuroprotective	Blocks 11-HSD1 enzyme activity	Decrease cortisol production and neurodegeneration (DMT)	NCT02727699	Recruiting	Actinogen Medical, ICON Clinical Research	March-17	March-19

Abbreviations: ADCS, Alzheimer's Disease Cooperative Study; ADDF, Alzheimer's Drug Discovery Foundation; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; APOE, apolipoprotein E; APP, amyloid precursor protein; ATRI, Alzheimer's Therapeutic Research Institute; BACE, Beta-site Amyloid precursor protein Cleaving Enzyme; cAMP, cyclic adenosine monophosphate; CB, cannabinoid; DMT, disease-modifying therapy; GM-CSF, granulocyte-macrophage colony-stimulating factor; GSK, GlaxoSmithKline; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme; HSD, hydroxysteroid dehydrogenase; HT, hydroxytriptamine; hUCB-MSCs, human umbilical cord-derived mesenchymal stem cells; MAPK, mitogen-activated protein kinase; NIA, National Institute on Aging; NMDA, N-methyl-D-aspartate; PPAR, peroxisome proliferator-activated receptor; SNRI, serotonin-norepinephrine reuptake inhibitors.

NOTE. Sixty-three agents in 75 phase II clinical trials currently ongoing as of January 30, 2018 according to clinicaltrials.gov.

NOTE. Bolded terms represent new entries into the 2018 phase II pipeline.

*Phase I/II trials.

with AD. Immunotherapies have the potential for long-term modification of the immune system, making participation of normal controls impermissible; these agents are typically assessed in patients with AD in phase I. Phase I includes single ascending dose trials assessing gradually increasing single doses and multiple ascending dose trials where individuals receive doses for 14–28 days [14–16]. Single ascending dose and multiple ascending dose studies usually include cohorts of 6–12 individuals assigned to drug or placebo (commonly four on placebo and eight on drug in a 12 person cohort). Food effects on drug absorption and drug-drug interactions are also assessed in phase I studies.

There are 23 agents in 25 trials in phase I. Of these, there were 17 DMTs, four cognitive-enhancing agents, and two agents of unknown MOA. No agents addressing neuropsychiatric symptoms were included. Of the 17 DMTs in phase I in 2018 (Fig. 1; Table 4), five were immunotherapies directed at amyloid-related targets, four had tau-related MOAs, one addressed both amyloid and tau targets, and seven had other mechanisms (e.g., neuroprotection, metabolic, regenerative, or anti-inflammatory). The MOA was not identified for two agents.

Phase I trials had an average duration of 982 days or 140 weeks (recruitment and treatment period) and included a mean number of 73 participants in each trial.

3.5. Trial sponsors

Across all trials, 56.6% are sponsored by the biopharma industry, 31.6% by Academic Medical Centers (with funding from National Institutes of Health, industry, or other entities), and 8.8% by others. Table 5 shows the sponsor of agents is different by trial phases.

3.6. Biomarkers

Table 6 shows the biomarkers used as outcome measures in current phase II and phase III AD clinical trials as described in the federal website; not all trial descriptions in clinicaltrials.gov note if biomarkers are included in the trial.

AD biomarkers served as secondary outcomes in 18 phase III DMT trials and 20 phase II DMT trials. The most common biomarkers used were CSF amyloid, CSF tau, volumetric magnetic resonance imaging, and amyloid PET. One study reported using tau PET as a secondary outcome.

Amyloid biomarkers can be used to establish the presence of amyloid abnormalities and support the diagnosis of AD. Of the 25 phase III DMT trials, five trials used amyloid-PET as an entry criterion, two used CSF-amyloid, and seven used either amyloid-PET or CSF-amyloid. Ten out of 38 phase II DMT trials used amyloid-PET as an entry criterion, five used CSF-amyloid, and two used either amyloid-PET or CSF-amyloid. Eleven DMT trials in phase III and 21 in

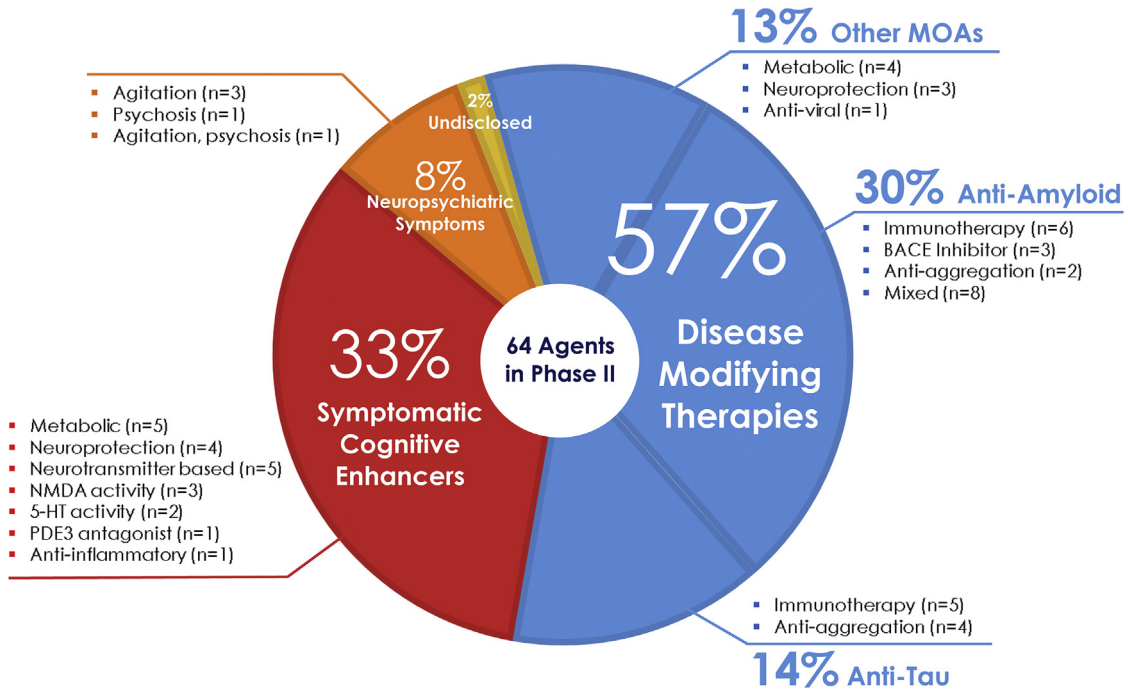

Fig. 3. Mechanisms of action of agents in phase II.

phase II did not require biomarker confirmation of AD for trial entry.

3.7. Comparison to 2017 pipeline

Compared with the 2017 pipeline, there are four new agents in phase III (AXS-05, octohydroaminoacridine succinate, escitalopram, and zolpidem), 14 in phase II (BIIB092, deferiprone, DHP1401, GV1001, ID1201, IONIS MAPTRx, LM11A-31-BHS, LY3002813, MLC901, MP-101, montelukast, VX-745, RO7105705, and rotigotine), and eight in phase I (NDX-1017, salsalate, vorinostat, BIIB076, JNJ-63733657, NP001, NPT088, and AGN-242071). Only one of the four new agents in phase III, (octohydroaminoacridine succinate) was previously present in phase II. Of the new agents in phase II, three of the 14 were previously noted in phase I (LY3002813, RO7105705, and VX-745). There are seven repurposed agents in phase III and 24 in phase II of the AD pipeline.

Eight agents listed in phase III in 2017 [7] failed in clinical trials as of January 30, 2018. These included the 5-HT6 inhibitors idalopirdine and intepirdine [17]. Three trials studying solanezumab (EXPEDITION studies) in prodromal/mild AD have been terminated as the study's primary end point was not met. The TOMMORROW studies (TOMM40301 and 303) studying pioglitazone were terminated in early 2018. Other trials failing to meet their primary outcomes included AC-1204, aripiprazole, MK-8931, nilvadipine and azeliragon. Two phase III trials for brexpiprazole as treatment for agitation in AD have completed and a third phase III trial is planned to begin in 2018.

Six agents were listed in phase II in 2017 and are not listed in any phase in 2018 and are no longer in development at this time (they could re-enter development). Trials of four agents were completed in 2017 and are not listed in the 2018 pipeline: BI409306, adenosine triphosphate, PQ912, and T-817MA. The trial status for NewGam 10% intravenous immunoglobulin changed to "unknown" because it has not been updated for more than 2 years on clinicaltrials.gov. Trials for the following five agents in phase I in 2017 were either completed or terminated and are not listed in the 2018 pipeline: BPN14770, PF-06751979, NGP 555, HTL0009936, and LY2599666.

4. Discussion

The Food and Drug Administration approved 46 new drugs (not including new doses, new formulations, or combinations of existing agents) in 2017. Six agents were approved for central nervous system disorders: edaravone for amyotrophic lateral sclerosis, cerliponase alfa for Batten disease, valbenazine for tardive dyskinesia, deutetrabenazine for chorea associated with Huntington's disease, ocrelizumab for relapsing-remitting and primary progressive multiple sclerosis, and safinamide for patients with Parkinson's disease experiencing "off" episodes (https://fda.gov/drugs/DevelopmentApprovalProcess). Three of these agents are DMTs (edaravone, cerliponase alfa, and ocrelizumab), and three are symptomatic therapies for amelioration of motor disorders. There were no new drug

Table 4
Agents currently in phase I of Alzheimer's disease drug development (as of 1/30/2018)

Agent	Agent mechanism class	Mechanism of action	Therapeutic purpose	Clinicaltrials.gov ID	Status	Sponsor	Start date	Estimated end date
Aducanumab	Anti-amyloid	Monoclonal antibody	Remove amyloid (DMT)	NCT01677572	Active, not recruiting	Biogen	October-12	October-19
AGN-242071	Undisclosed	Undisclosed	Undisclosed	**NCT03316898**	Not yet recruiting	Allergan	November-17	June-18
Allopregnanolone injection	Metabolic, neuroprotective	GABA receptor modulator	Improve neurogenesis (cognitive enhancer)	NCT02221622	Recruiting	University of Southern California, NIA	August-14	December-17
BIIB076	Anti-tau	Monoclonal antibody	Remove tau (DMT)	**NCT03056729**	Recruiting	Biogen	February-17	April-19
Bisnorcymserine (BNC)	Neurotransmitter based	Butyrylcholinesterase inhibitor	Acetylcholine neurotransmission (cognitive enhancer)	NCT01747213	Recruiting	NIA	January-13	July-18
Crenezumab	Anti-amyloid	Monoclonal antibody	Remove amyloid (DMT)	NCT02353598	Active, not recruiting	Genentech	February-15	September-23
hMSCs	Regenerative	Stem cell therapy	Regenerate neurons	NCT02600130	Recruiting	Longeveron LLC	August-16	October-19
Idalopirdine (Lu AE58054)	Neurotransmitter based	5-HT6 receptor antagonist	Improve neuronal signaling (cognitive enhancer)	**NCT03307993**	Recruiting	H. Lundbeck A/S	September-17	January-18
Insulin aspart (Intranasal)	Metabolic	Increases insulin signaling in the brain	Enhance cell signaling and growth (cognitive enhancer)	NCT02462161	Recruiting	Wake Forest School of Medicine, NIA, General Electric	May-15	July-18
JNJ-63733657	Anti-tau	Monoclonal antibody	Remove tau (DMT)	**NCT03375697**	Recruiting	Janssen	January-18	February-19
KHK6640	Anti-amyloid	Anti-Aβ peptide antibody	Remove amyloid (DMT)	**NCT03093519**	Active, not recruiting	Kyowa Hakko Kirin Co.	March-17	June-18
Lu AF20513	Anti-amyloid	Polyclonal antibody	Remove amyloid (DMT)	NCT02388152	Active, not recruiting	H. Lundbeck A/S	March-15	October-18
LY3002813	Anti-amyloid	Monoclonal antibody	Remove amyloid (DMT)	NCT02624778	Recruiting	Eli Lilly and Company	December-15	June-20
LY3303560	Anti-tau	Monoclonal antibody	Remove tau (DMT)	NCT02754830	Recruiting	Eli Lilly and Company	April-16	April-18
				NCT03019536	Recruiting	Eli Lilly and Company	January-17	February-20
NDX-1017	Regenerative	Hepatocyte growth factor	Regenerate neurons	**NCT03298672**	Recruiting	M3 Biotechnology, ADDF, Biotrial Inc.	October-17	June-18
NP001	Anti-inflammatory	Immune regulator of inflammatory monocytes/ macrophages	Activate immune system (DMT)	**NCT03179501**	Recruiting	Neuraltus Pharmaceuticals, University of Hawaii	September-17	December-17
NPT088	Anti-amyloid, Anti-tau	IgG1 Fc-GAIM fusion protein	Clear amyloid and tau (DMT)	**NCT03008161**	Recruiting	Proclara Biosciences	December-16	December-18
Oxaloacetate (OAA)	Metabolic	Mitochondrial enhancer	Enhance multiple cellular processes (DMT)	NCT02593318	Recruiting	University of Kansas Medical Center	October-15	October-18
RGN1016	Undisclosed	Undisclosed mechanism	Undisclosed	NCT02820155	Recruiting	National Taiwan University	June-16	February-17

(*Continued*)

Table 4
Agents currently in phase I of Alzheimer's disease drug development (as of 1/30/2018) (*Continued*)

Agent	Agent mechanism class	Mechanism of action	Therapeutic purpose	Clinicaltrials.gov ID	Status	Sponsor	Start date	Estimated end date
Salsalate	Anti-inflammatory	Non-steroidal anti-inflammatory	Reduce neuronal injury (DMT)	**NCT03277573**	Recruiting	University of California, San Francisco	July-17	October-18
TAK-071	Neurotransmitter based	Muscarinic M1 receptor modulator	Enhance acetylcholine neurotransmission (cognitive enhancer)	NCT02769065	Recruiting	Takeda	May-16	March-18
Telmisartan	Neuroprotective, anti-inflammatory	Angiotensin II receptor blocker, PPAR-gamma agonist	Improve vascular functioning and effects on amyloid pathology (DMT)	NCT02471833	Recruiting	Emory University	April-15	March-18
TPI-287	Anti-tau	Microtubule protein modulator	Reduce tau-mediated cellular damage (DMT)	NCT01966666	Active, not recruiting	University of California, San Francisco	November-13	November-17
Vorinostat	Neuroprotective	Histone deacetylase inhibitor	Enhance multiple cellular processes including tau aggregation and amyloid deposition (DMT)	**NCT03056495**	Recruiting	German Center for Neurodegenerative Diseases, University Hospital, Bonn, University of Gottingen	September-17	October-19

Abbreviations: ADDF, Alzheimer's Drug Discovery Foundation; BACE, Beta-site Amyloid precursor protein Cleaving Enzyme; DMT, disease-modifying therapy; GABA, gamma-aminobutyric acid; hMSCs, human mesenchymal stem cells; NIA, National Institute on Aging; PPAR, peroxisome proliferator-activated receptor.

NOTE. Twenty-three agents in 25 phase I clinical trials currently ongoing as of January 30, 2018 according to clinicaltrials.gov.

NOTE. Bolded terms represent new entries into the 2018 phase I pipeline.

Table 5
Trial sponsor for each phase of development

Sponsor	N of trials (%)		
	Phase I	Phase II	Phase III
Biopharma	13 (52.0)	37 (49.3)	26 (74.3)
Academic Medical Centers	6 (24.0)	19 (25.3)	3 (8.6)
National Institutes of Health (NIH)	1 (4.0)	0	0
NIH and industry	0	2 (2.7)	0
Consortium/foundation	0	3 (4.0)	0
NIH and Academic Medical Centers	2 (8.0)	3 (4.0)	2 (5.7)
Industry and consortium/foundation	2 (8.0)	2 (2.7)	1 (2.9)
Other combinations	1 (4.0)	9 (12.0)	3 (8.6)

approvals for treatment of AD; none have been approved since 2003 [5].

Review of the 2018 AD drug development pipeline shows that most agents have MOAs directed at disease modification (63% across all phases); 23% are cognitive-enhancing agents, and 12% are drugs directed at controlling neuropsychiatric symptoms (three agents have undisclosed MOAs). A few new agents have entered the pipeline when compared with the 2017 review [7]: there are eight new agents in phase I, 14 in phase II, and four in phase III. Several agents have exited the pipeline including: five in phase I, five in phase II, and eight in phase III.

5-hyroxytryptamine-6 receptor antagonists have represented a substantial segment of the AD drug development pipeline with several agents exploring this cognitive enhancing mechanism. SAM-531 (also PF-052-12365) was assessed in a clinical trial of patients with mild-moderate AD not on therapy with memantine or a cholinesterase inhibitor. The trial was interrupted after an interim analysis suggested that all doses in the trial were futile. SB742457 (intepirdine) had evidence of efficacy in a phase II clinical trial [18] but failed to meet primary outcomes in a more recent phase III trial [19]. Similarly, LU-AE-58054 (idalopirdine) achieved a significant benefit on the Alzheimer's Disease Assessment Scale–Cognitive Subscale [20] in phase II but failed to meet its primary outcomes in three phase III trials [17]. Other agents in this class are currently in trials (Suvn-502) or have shown efficacy in preclinical models (PRX-07034Z) [21]. Although recent trials have not demonstrated a drug-placebo difference with 5-HT6 antagonists, unresolved issues regarding the diagnosis of AD in trials not requiring biomarker confirmation, failure of decline of placebo groups in some trials, recruitment of atypical forms of AD (due to exclusion of standard of care with memantine and cholinesterase inhibitors), and dose preclude definitive conclusions about efficacy of this mechanism based on the existing trials.

Phosphodiesterases (PDEs) comprise a group of 11 families of enzymes that regulate cyclic adenosine monophosphate and cyclic guanosine monophosphate and are involved in neuroplasticity and memory consolidation [22–25]. Several PDE inhibitors have been assessed in clinical trials of AD or MCI [26], and there are currently three PDE inhibitors in phase I and three in phase II. Three of the agents are PDE9 inhibitors, two are PDE 4 inhibitors, and 1 is a PDE 3 inhibitor. Trial outcomes will determine if PDE inhibitors produce cognitive benefit, if inhibition of one of the enzymes is more effective, and what population of patients is more benefited by treatment.

Biomarkers are important for the develeopment of both symptomatic and disease-modifying drugs. The use of biomarkers has become widespread in trials of DMTs, but biomarkers for symptomatic agents are more unusual. PDE9 inhibitors reduce CSF cyclic guanosine monophosphate, a second messenger that activates intracellular protein kinases. Measures of cyclic guanosine monophosphate have been used as a translational biomarker to establish target engagement and dose-response relationships in both humans and nonhuman primates [27,28].

An increasing number of agents are directed at tau-related targets. Neurofibillary tangles, consisting of aggregates of phosphorylated microtubule-associated tau protein, are one of two major pathological hallmarks of AD [1,2,29]. Seminal clinicopathological correlation studies conducted by Braak and Braak [30], demonstrating that neurofibrillary tangle burden more closely correlate with cognitive decline than amyloid plaque load, indicate that agents directed against aberrant tau protein could serve as important anti-AD agents. Normal tau protein goes through multiple biological transformations in AD, and strategies to target tau are diverse. Fig. 4 depicts tau's role in AD pathogenesis and shows the purported MOA of candidate therapies directed at tau biology.

Tau remains an important but largely untested target for disease modification in AD. The first anti-tau programs were directed at reducing tau aggregation. The preliminary results of these studies were largely disappointing, and agents directed against tau aggregation are being re-evaluated [31]. More recently, immunotherapy strategies have achieved ascendency in the pipeline with seven tau immunotherapies entering phase I or II testing. Among the unknowns for tau immunotherapy programs are: (1) which is the most

Table 6
Biomarkers as outcome measures in phase II and phase III trials for agents in the Alzheimer's disease drug development pipeline (clinicaltrials.gov; January 30, 2018)

Biomarker	N of trials (%)	
	Phase III	Phase II
CSF amyloid	13 (37.1)	17 (22.7)
CSF tau	14 (40.0)	17 (22.7)
FDG-PET	5 (14.3)	10 (13.3)
vMRI	9 (25.7)	7 (9.3)
Plasma amyloid	2 (5.7)	5 (6.7)
Plasma tau	0	1 (1.3)
Amyloid PET	11 (31.4)	8 (10.7)
Tau PET	0	1 (1.3)

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

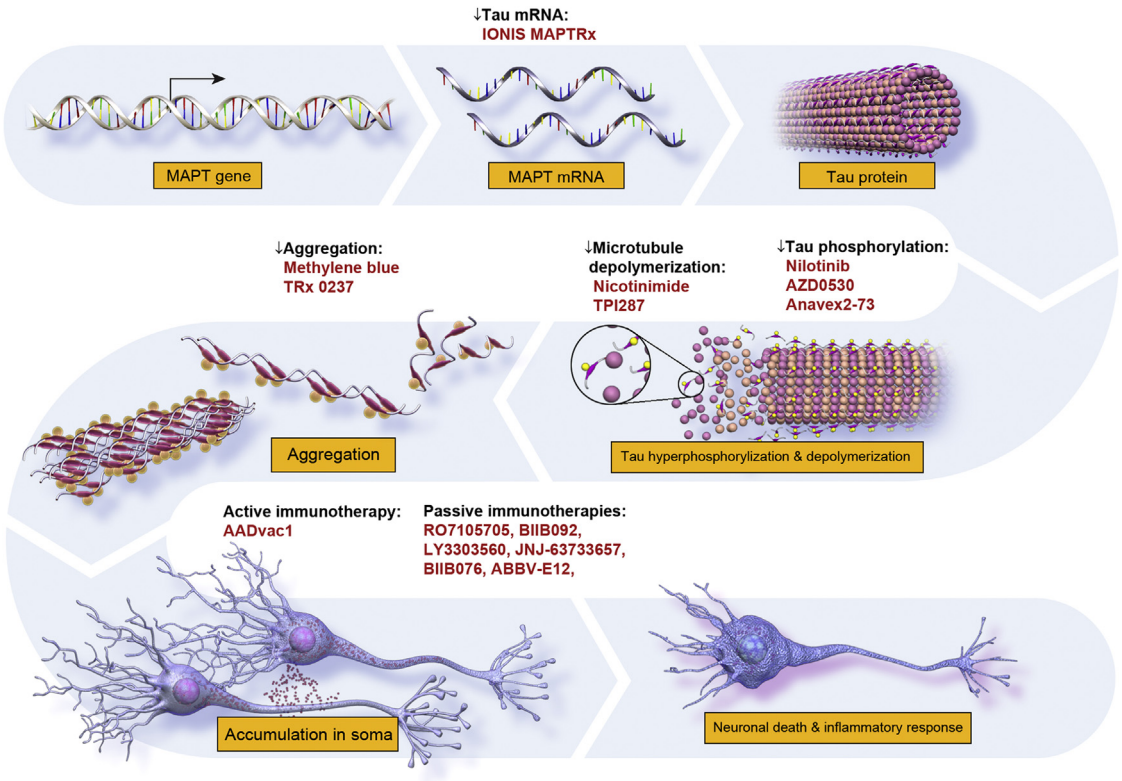

Fig. 4. Site of action of anti-tau agents.

appropriate tau epitope to target, (2) what site of activity is required for effectiveness (intraneuronal vs. extracellular), and (3) what level of target engagement is required for efficacy [32]. The emergence of tau radioligands detectable by PET may provide key insights into these questions [33]; this technology remains expensive, has limited availability, and understanding of its interpretation is evolving.

A concerning observation derived from this AD pipeline review is the lack of agents targeting the moderate to advanced stages of AD. Only 26 trials permit inclusion of participants with scores of 14 or less, and only 12 include participants with scores of 10 or less. Together, these studies intend to enroll only 1720 participants. With over 15 million people affected by AD dementia worldwide [34], there is an urgent need to develop more effective symptomatic treatments for moderate to advanced stage disease. The paucity of agents directed at this population represents a significant weakness of the AD drug development pipeline.

A challenge for AD drug development is the lack of surrogate biomarkers. Surrogate markers—measures of disease that can be substituted for a clinical end point (i.e., hemoglobin A1c in diabetes)—predict clinical outcomes and accelerate drug development [35]. In the current AD landscape, there are few biomarkers and no accepted surrogate markers. The primary utility of existing AD biomarkers is to improve diagnostic accuracy [36], and these have been incorporated into current research criteria [37–39]. Previous research shows that misdiagnose rates in AD clinical trials can exceed 20% [40] and could contribute importantly to trial failure. Diagnostic verification is particularly important in trials of DMTs. Review of the 2018 pipeline reveals that a surprisingly low percentage of trials of DMTs require diagnostic biomarkers for entry or as secondary outcomes. The development and use of biomarkers for AD clinical trials remain a crucial unmet goal for the field.

Successful drug development requires effective recruitment of clinical trial participants and efficient execution of clinical trials in addition to drugs that are produced by rigorous disciplined drug development processes. Challenges of recruitment have become especially acute as prevention trials have become more numerous. Participants are cognitively normal, are not health-care seeking, and may not know their risk status. There are currently several efforts in the AD drug development arena that address these critical issues. Online registries are increasingly used to identify and educate possible trial participants. These registries vary in nature, with some collecting a minimum of information (age, interest in trials) and others collecting extensive cognitive, clinical, and demographic information [41,42]. The over-arching purpose of these registries is to identify interested individuals that can be assessed for appropriateness for clinical trials and enlist them if they have the prespecified biomarker profile required for trial participation. Optimizing the use of registries to enhance trial

recruitment will be among the important lessons from studying the current registries.

Clinical trial efficiency can be improved with more rapid clinical trial site start up (facility review, budget acceptance, and so on), pre-certified raters, use of a single institutional review board, and rapid recruitment of appropriate participants. Addressing each of these aspects of efficient trial site function can help accelerate clinical trial execution and drug development. In the United States, the Global Alzheimer Platform, the National Institutes of Health, the Alzheimer's Association TrialMatch program, the Alzheimer's Clinical Trial Consortium, and other initiatives are striving to improve trial efficiency [41,43]. In Europe, the European Prevention of Alzheimer's Dementia program is part of the Innovative Medicines Initiative and is addressing many of the same issues, especially as they apply to phase II clinical trials [44].

Clinicaltrials.gov has shortcomings that are important to recognize when considering the data presented here. The information provided may not represent the entire universe of AD drug development: not all phase I trials, especially those conducted outside the United States, may be registered in the database 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 the trial [9], but not all sponsors may meet this deadline. The Food and Drug Administration 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 [45]; recent reviews show a high rate of compliance with the registration rules [10–12]. The clinicaltrials.gov database is the most comprehensive of any existing trial database and provides credible data for drawing conclusions about AD drug development. 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 on January 30, 2018).

This review of the 2018 AD drug development pipeline demonstrates the continuing commitment of the scientific community, pharmaceutical industry, and regulatory agencies to develop new drugs of AD. Trends evidenced in the 2018 pipeline include more trials in preclinical and prodromal populations and greater use of biomarkers to support the diagnosis of AD. Every trial is a learning opportunity and informs the drug development process. Success depends on establishing targets critical to the disease process, developing efficacious agents, and conducting trials rigorously.

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RESEARCH IN CONTEXT

1. Systematic review: New treatments for Alzheimer's disease (AD) are urgently needed. The drug development process progresses from phase I to phase II and phase III. Trials are listed on the federal government database clinicaltrials.gov.
2. Interpretation: A study of the clinicaltrials.gov database reveals that there are 112 agents in the pipeline; of these, 26 are in phase III, 63 in phase II, and 23 in phase I. More tau-related targets are included for drugs in the current pipeline than previously. Clinical trial organizations are evolving to support clinical trial performance.
3. Future directions: More agents are required in the pipeline to assure successful development of new treatments for AD. The number and success of pipeline agents depends on basic science research and efficient trials.

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