Will the Next Five Years Witness an Innovation Wave in Medicines for Alzheimer's?

The Healthcare System Is Not Ready for New Alzheimer's Drugs

Success in drug development for Alzheimer's disease has been elusive. Recent analysis has shown a near 100% failure rate in the past decade. Yet, each failed trial advances the science and presents the opportunity to apply new insights. As a result, there are a significant number of compounds in Phase 3, the final stage of drug development. Seventeen drugs in this final stage are likely to finish testing and could be available to people with the disease in the next five years. These findings are based on the analysis led by ResearchersAgainstAlzheimer's, a global network of leading Alzheimer's researchers at top academic institutions and corporations.

Our analysis leads us to be cautiously optimistic that innovative treatments are within our reach. We need to make sure the healthcare system is ready.

Understanding the Alzheimer's Drug Development Pipeline

Robust Alzheimer's Pipeline Offers Promise for Treatment – Despite Recent Track Record

MORE THAN A DECADE SINCE A NOVEL ALZHEIMER'S DRUG WAS APPROVED

Namenda was approved by the FDA in 2003, marking the last time a novel Alzheimer's therapy reached the market.[1]

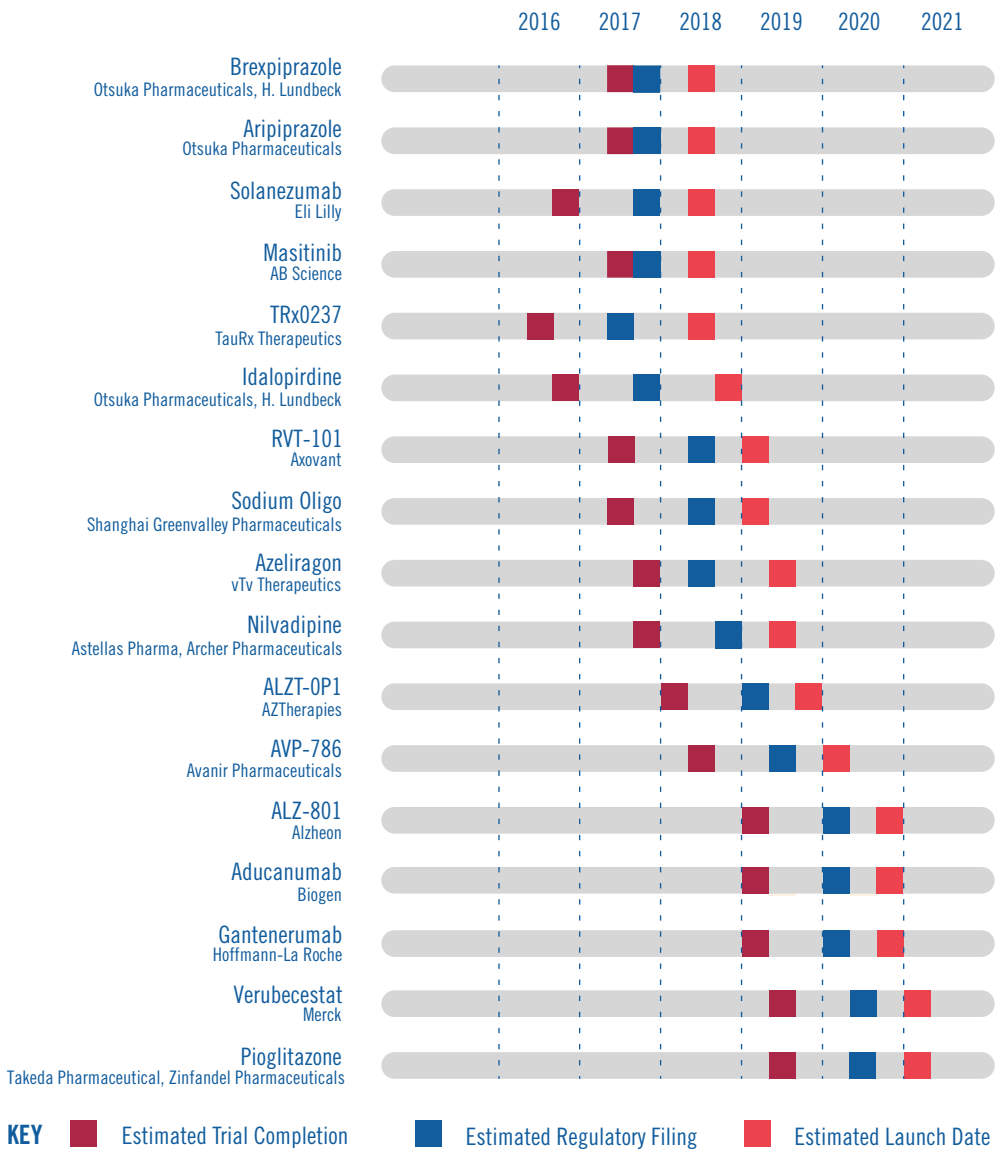
PIPELINE OUTLOOK

There are approximately 50 drugs in Phase 2 trials and about a dozen drugs in Phase 2/3 trials.[2]

ROUTE OF ADMINISTRATION

Several of these new, innovative treatments will be administered by infusion – bringing new requirements for settings of care.

Phase 3 Drugs in Development That Could Launch in the Next Five Years



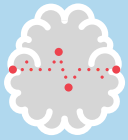
Alzheimer's Is a Growing Threat Across the Globe

ALZHEIMER'S IMPACTS THE U.S ON A MASSIVE SCALE.

In 2015, 5.3 million Americans were suffering from Alzheimer's – and 5.1 million of them were over 65.[3] Each year, dementia costs the United States roughly $200 billion[4] – or roughly 42 percent of the 2015 U.S. budget deficit.[5]

THE NUMBER OF PEOPLE SUFFERING FROM DEMENTIA IS GROWING.

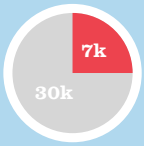
Today, 46.8 million people around the world suffer from dementia[6], and by 2030, it's predicted that 74.7 million people will suffer from the disease.[7] Experts estimate that care for people with dementia costs roughly 1 percent of global GDP.[8]



ALZHEIMER'S: A LEADING CAUSE OF DEATH.

Recent research shows that Alzheimer's disease is the 3rd leading cause of death in the United States after heart disease and cancer.[9] In fact, a new patient develops the disease every 67 seconds in the U.S.[10] and every three seconds around the world.[11] And it's the only "top 10" cause of death in America that can't be prevented, stopped or slowed.[12]

America's Healthcare System Is Not Prepared for New Alzheimer's Treatments



SHORTAGE OF TRAINING FOR FRONTLINE PHYSICIANS TO CARE FOR AN AGING SOCIETY. Today, there are 7,000 practicing American geriatricians, but new research shows that the country will need at least 30,000 geriatricians by 2030 to adequately aid America's aging population.[13] And, according to the American Geriatrics Society, few medical students are choosing geriatrics – only 75 medical resident students entered geriatric medicine fellowships in 2010, compared to 112 in 2005 – a 33 percent decrease.[14]

INNOVATIONS IN ALZHEIMER'S TREATMENTS MUST BE COUPLED WITH PATIENT-ORIENTED REIMBURSEMENT.
A recent innovation in Alzheimer's to be granted FDA approval, a diagnostic called Amyvid, received limited support from Centers for Medicare and Medicaid Services, the main payer of treatments for people living with Alzheimer's disease, and strict reimbursement restrictions. Will payers understand the value proposition of future innovations and give broad access? The track record to date gives us concern.

PATIENTS NOT ALWAYS INFORMED.
Fewer than half (45 percent) of people with Alzheimer's have been informed of their diagnosis by a doctor; in contrast, a vast majority (90 percent) of people with cancer and cardiovascular disease have been given a diagnosis by their doctor.[15] While this likely varies based on the setting of care, improving diagnosis rates is critical to advancing both care and research.

LONG WAIT TIMES TO SEE NEUROLOGISTS.
In 2012, the average wait time to see a neurologist was 35 business days – compared to 28 business days in 2010, a 25 percent increase.[16]
A study from 2014 shows that average wait times for cardiologists was 16.8 days – about 50 percent less than the wait times to see a neurologist.[17]

ALZHEIMER'S COMMONLY MISDIAGNOSED.
In some settings, up to half of all cases of Alzheimer's disease are misdiagnosed.[18]
Visits to memory care specialists in neurology, psychiatry or geriatrics are encouraged.

Methodology

This analysis was constructed through extensive research and interviews, including interviews with company executives about publicly available information, SEC filings, company reports, presentations at medical conferences and media coverage. Additionally, academic research experts and select ResearchersAgainstAlzheimer's (RA2) members provided input and review of the analysis. However, the responsibility for the content of this report belongs solely to UsAgainstAlzheimer's, the convener of RA2, and not to any other organization or individual. When complete information pertaining to compound development milestones was not available, the research team estimated the timing of milestones based on our experience in pharmaceutical drug development. Information presented in this analysis does not include drugs that are in Phase 2/3 or earlier clinical trials. This report focuses only on drugs in Phase 3 clinical trials. This information is subject to change given the nature of clinical trials and drug development. Our intention is to provide regular updates on the status of drug development in Alzheimer's, and we welcome input and corrections.

PIPELINE ANALYSIS

Product Name	Manufacturer	Route of Administration	MOA (Mechanism of Action)	Phase of Drug Development	Target Population	Length of Current Trial	Number of Trial Participants	Estimated Trial Completion	Estimated Regulatory Filing	Estimated Launch Date
Aducanumab	Biogen	Infusion	anti-Abeta mAb	Phase 3 (ENGAGE and EMERGE)	People with MCI due to Alzheimer's disease or mild Alzheimer's disease as ascertained by a positive amyloid PET scan (Trials 1 and 2)	18 months (Trials 1 and 2)	1,350 participants (Trials 1 and 2)	First half of 2019 (Trials 1 and 2)	Q1 2020	Q3 2020
ALZ-801	Alzheon	Oral	Oral inhibitor of amyloid aggregation and neurotoxicity	Phase 3	APOE4/4 homozygous Alzheimer's patients	18 months	Unknown	Q1 2019	Q1 2020	Second half of 2020
ALZT-0P1	AZTherapies	Oral	The first drug inhibits beta-amyloid peptide polymerization and lowers cytokine production. The second inhibits the neuroinflammatory response.	Phase 3	Subjects with evidence of early Alzheimer's disease	72 weeks	600 participants	March 2018 (Q1)	March 2019 (Q1)	Q4 2019
Aripiprazole	Otsuka Pharmaceuticals	Oral	Dopamine partial agonist	Phase 3	Patients with agitation associated with dementia of the Alzheimer's type	10 weeks	880 participants	July 2017 (Q3)	Late 2017	First half of 2018
AVP-786	Avanir Pharmaceuticals	Oral	Novel investigational drug product consisting of a combination of deuterium modified dextromethorphan and ultra-low dose quinidine, used as a metabolic inhibitor	Phase 3	Treatment of agitation in patients with dementia of the Alzheimer's type (Trials 1,2,3)	12 weeks (Trials 1 and 2) 52 weeks (Trial 3)	380 participants (Trial 1) 325 participants (Trial 2) 550 participants (Trial 3)	July 2018 (Trials 1 and 2) July 2019 (Trial 3)	July 2019 (Q3)	Q1 2020
Azeliragon	vTv Therapeutics	Oral	RAGE antagonist	Phase 3	People with clinical diagnosis of mild probable Alzheimer's disease. (Trials 1 and 2)	18 months (Trials 1 and 2)	400 participants (Trials 1 and 2)	Q4 2017 (sub-study A) (Trial 1) Q2 2018 (sub-study B) (Trial 2)	2018	Q2 2019
Brexpiprazole	Otsuka Pharmaceuticals	Oral	Dopamine receptor D2 partial agonist	Phase 3	Treatment of agitation in patients with Alzheimer's dementia (Trials 1 and 2)	12 weeks (Trials 1 and 2)	420 participants (Trial 1) 230 participants (Trial 2)	June 2017 (Q2) (Trials 1 and 2)	December 2017 (Q4)	June 2018 (Q2)
Crenezumab	Hoffmann-La Roche	Infusion	Fully humanised, monoclonal antibody designed to target all forms of beta amyloid	Phase 3	People with prodromal to mild Alzheimer's disease	100 weeks	750 participants	2021	July 2022 (Q3)	Q1 2023

PIPELINE ANALYSIS (CONT.)

Product Name	Manufacturer	Route of Administration	MOA (Mechanism of Action)		Target Population	Length of Current Trial	Number of Trial Participants	Estimated Trial Completion	Estimated Regulatory Filing	Estimated Launch Date
Gantenerumab	Hoffmann-La Roche	Infusion	IgG1 antibody designed to bind with subnanomolar affinity to a conformational epitope on Aβ fibrils.	Phase 3 (Trial 1) Phase 2/3 (DIAN TU) (Trial 2) Phase 3 (Trial 3)	Patients with mild Alzheimer's disease. (Trial1) People with an inherited autosomal-dominant mutation in APP, presenilin-1, or presenilin-2. (Trial 2) Patients with prodromal Alzheimer's disease. (Trial 3)	Subcutaneous injections every 4 weeks up to week 100. (Trial 1) Phase 1: 2 years Phase 2: 3 years. (Trial 2) Subcutaneous injections every 4 weeks up to week 104. (Trial 3)	1,000 participants planned (Trial 1) 210 participants (Trial 2) 799 participants (Trial 3)	Trial being converted to open-label to explore higher dose regimens. For its analysis of estimated regulatory filing and launch date, RA2 used March 2019 as the estimated trial completion date, which is based off information from clinicaltrials.gov. (Trial 1) December 2019 (Q4). (Trial 2) Trial being converted to open-label to explore higher dose regimens. (Trial 3)	March 2020	Q4 2020
Idalopirdine	H. Lundbeck	Oral	Serotonin 6 (5-HT6) receptor antagonist	Phase 3	Patients with mild to moderate Alzheimer's disease who are already taking a stable dose of 10 mg/day of donepezil. (Trials 1,2, and 4) Patients with mild to moderate Alzheimer's disease who are already taking a stable dose of 10 mg/day of an acetylcholinesterase inhibitor. (Trial 3)	24 weeks (Trials 1,2, and 3) 28 weeks (Trial 4)	930 participants (Trial 1) 840 participants (Trial 2) 720 participants (Trial 3) 1,770 participants (Trial 4)	October 2016 (Q4) (estimated primary completion date) (Trial 1) March 2017 (Q1) (Trials 2 and 3) October 2017 (Q4) (Trial 4)	September/ October 2017	End of 2018
Masitinib	AB Science	Oral	Targeting of Mast Cell through c-Kit inhibition Targeting of Tau through Fyn inhibition	Phase 3	Patients with mild to moderate Alzheimer's disease	6 months	675 participants	Interim analysis planned Q3 2017 and Final analysis planned in 2018	Q4 2017 if interim analysis is positive	2018 if interim analysis is positive and approval granted by the authorities
Methylpheni-date	National Institute on Aging, Johns Hopkins Bloomberg School of Public Health	Oral	Inhibits the reuptake of dopamine and norepinephrine	Phase 3	Treatment for clinically significant apathy in Alzheimer's disease patients	6 months	200 participants	August 2020 (Q3)	August 2021 (Q3)	April 2022 (Q2)
Nilvadipine	Astellas Pharma and Archer Pharmaceuticals, Inc.	Oral	Dihydropyridine calcium channel blocker	Phase 3	Patients with mild to moderate Alzheimer's disease	18 months	500 participants	December 2017 (Q4)	December 2018 (Q4)	Q3 2019
Pioglitazone	Takeda Pharmaceutical Company, Zinfandel Pharmaceuticals	Oral	Insulin sensitizer of the thiazolidinedione class of peroxisome-proliferator activated receptor γ (PPARγ) agonists.	Phase 3	Cognitively-normal people who are at high-risk of developing Mild Cognitive Impairment due to Alzheimer's Disease. (Trial 1) Participants with mild cognitive impairment due to Alzheimer's disease. (Trial 2)	5 years (Trial 1) 2 years (Trial 2)	3,500 participants (Trial 1) 316 participants (Trial 2)	July 2019 (Q3) (Trial 1) April 2021 (Q2) (Trial 2)	July 2020 (Q3)	Q1 2021
RVT-101	Axovant	Oral	5HT-6 antagonist	Phase 3	Patients with mild to moderate Alzheimer's disease	24 weeks	1,150 participants	Second half of 2017	Second half of 2018	Q1 2019

PIPELINE ANALYSIS (CONT.)

Product Name	Manufacturer	Route of Administration	MOA (Mechanism of Action)	Phase of Drug Development	Target Population	Length of Current Trial	Number of Trial Participants	Estimated Trial Completion	Estimated Regulatory Filing	Estimated Launch Date
Sodium Oligo-mannurarate	Shanghai Greenvalley Pharmaceutical Co.	Unknown	Oligosaccharide that binds to more than one region of amyloid-β (Aβ) and enhances clearance of the protein from the brain	Phase 3	Patients with mild to moderate Alzheimer's disease	36 weeks	788 participants	May 2017 (Q2)	May 2018 (Q2)	Q1 2019
Solanezumab	Eli Lilly	Infusion	Monoclonal antibody that binds to soluble monomeric forms of amyloid-beta	Phase 3 (EXPEDITION 3) (Trial 1) Phase 3 (EXPEDITION EXT) (Trial 2) Phase 2 (DIAN-TU) (Trial 3) Phase 3 (A4) (Trial 4)	Participants with mild Alzheimer's disease. (Trial 1) Patients with Alzheimer's disease. (Trial 2) People with an inherited autosomal-dominant mutation in APP, presenilin-1, or presenilin-2. (Trial 3) People who may be at risk for memory loss and cognitive decline due to Alzheimer's disease. (Trial 4)	80 weeks. (Trial 1) 400 mg administered once every 4 weeks by intravenous infusion (IV) for 100 weeks. (Trial 2) Phase 1: 2 years Phase 2: 3 years. (Trial 3) 400 mg solanezumab intravenously every 4 weeks for 168 weeks. (Trial 4)	2,100 participants (Trial 1) 1,275 participants (Trial 2) 210 participants (Trial 3) 1,150 participants (Trial 4)	October 2016 (Q4) (Estimated primary completion date) (Trial 1) November 2018 (Q4) (Trial 2) December 2019 (Q4) (Trial 3) April 2020 (Q2) (Trial 4)	October 2017 (Q4)	Q2 2018
TRx0237	TauRx Therapeutics	Oral	Second-generation tau protein aggregation inhibitor.	Phase 3	Patients with mild Alzheimer's disease with a CDR score of 0.5 or 1 and an MMSE of 20-26 (inclusive). (Trial 1) Patients with mild to moderate Alzheimer's disease with a CDR score of 1 to 2 and an MMSE of 14-26 (inclusive). (Trial 2) Patients with probable bvFTD who have frontotemporal atrophy confirmed by MRI and whose MMSE is 20 or higher. (Trial 3) Subjects completing Phase 3 studies above with Alzheimer's disease or Behavioral Variant Frontotemporal Dementia (bvFTD). (Trial 4)	18 months (Trial 1) 15 months (Trial 2) 12 months (Trial 3) 29 months (Trial 4)	800 participants (Trial 1) 890 participants (Trial 2) 220 participants (Trial 3) 1,300 participants (Trial 4)	August 2016 (Q3) (Trial 1) March 2016 (Q1) (Trial 2) April 2016 (Q2) (Trial 3) January 2017 (Q1) (Open-Label Extension Study) (Trial 4)	2017	2018
Verubecestat	Merck	Oral	Small-molecule inhibitor of BACE1 and BACE2	Phase 3	Participants with prodromal Alzheimer's disease. (Trial 1) Participants with mild to moderate Alzheimer's disease. (Trial 2)	104 weeks (Trial 1) 78 weeks (Trial 2)	1,500 participants (Trial 1) 1,960 participants (Trial 2)	July 2019 (Q3), primary completion date. (Trial 1) July 2017 (Q3), primary completion date. (Trial 2)	July 2020 (Q3)	Q1 2021

Based on expert interviews, AgeneBio's Levetiracetam could shortly enter Phase 3 clinical trials.

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Researchers4gainst Alzheimer's

ResearchersAgainstAlzheimer's (RA2) is a network of more than 400 Alzheimer's researchers established by UsAgainstAlzheimer's to advocate for federal research funding and policy reform in order to stop Alzheimer's disease. RA2 believes that an effective treatment for Alzheimer's is within reach if governments, industry, and citizens are willing to commit the resources and institute the policy changes that are necessary.

Us4gainst Alzheimer's

UsAgainstAlzheimer's (USA2) is an innovative non-profit organization demanding – and delivering – a solution to Alzheimer's. Driven by the suffering of millions of families, UsAgainstAlzheimer's presses for greater urgency from government, industry and the scientific community in the quest for an Alzheimer's cure – accomplishing this through effective leadership, collaborative advocacy, and strategic investments.

Our intention is to provide regular updates on the status of drug development in Alzheimer's, and we welcome input and corrections.

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