Pharma VOICE

THERAPEUTIC DIGEST

# ALZHEIMER'S DISEASE

IN COLLABORATION WITH thinkgen

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# Alzheimer's Disease

*Emerging Therapeutics in the Face of Challenges*

There are 5.1 million people with AD in the US and 13 million worldwide.

Alzheimer's disease (AD) is the sixth leading cause of death globally and the main reason for dementia in elderly people. AD is a long-term and progressive neurodegenerative disorder that steadily worsens memory and communication skills that eventually leads to disability. The need is urgent to find new drugs that will delay onset, slow progression, or improve symptoms of AD. However, as a neurodegenerative and age-related disorders that affect cognition, function, and behavior, AD is growing to staggering proportions as the global population ages. There are 5.1 million people with AD in the U.S. and 13 million worldwide. The prevalence of this disease is expected to increase to 13 million in the U.S. and more than 100 million worldwide by 2050[1]. The cost of care for AD domestically is estimated at $267 billion and this will balloon to more than $1 trillion per year by 2050 if new interventions are not developed. It is calculated that a delay in AD onset by 5 years would decrease the global population of people with AD by 5.7 million and decrease the expense of caring for those with AD by $367 million by 2050[2].

Unfortunately, numerous clinical trials exploring new therapeutic drugs have encountered disappointing outcomes in terms of improved cognitive performance since they are not capable of halting or stimulating the regeneration of already-damaged neural cells, and merely provide symptomatic relief. It has been extraordinarily difficult to develop new therapies for AD with a failure rate of greater than 99% and no new treatment has been approved since 2003[3]. Even though attempts to develop disease-modifying therapies (DMTs) for AD have had a 100% failure rate[4], every trial, however, presents opportunities to learn and improve the drug development process[5]. A deeper understanding of the AD therapeutic pipeline and the advances in trial methods may contribute to the development of novel and effective therapies in the future pipeline.

## CLASSES OF AGENTS IN ALZHEIMER'S DISEASE

There are four principal classes of agents in clinical trials for AD, including neuropsychiatric agents, cognition-enhancing drugs to improve cognition above baseline, DMTs that target underlying disease biology with the intent of delaying onset of cognitive symptoms or slow cognitive and functional decline, and combination therapies that include a DMT and cognition enhancer, or two or more DMTs.

## Principal classes of agents in trials for AD Table 1

| | |
|---|---|
| **Neuropsychiatric agents** | Psychosis (e.g. pimavanserin)<br>Agitation (e.g. AVP-786) |
| **Cognition enhancers** | 5-HT antagonists (e.g. SUV-502)<br>Cholinergic agents (e.g. CP-201) |
| **Disease-modifying therapies (DMT)** | Monoclonal antibodies (e.g. BAN2401)<br>Oral drugs (e.g. elenbecestat) |
| **Combination therapies** | DMT plus cognition enhancer or 2 or more DMTs |

*Source: Practical Neurology*

The average time to develop a drug for AD is 13 years and the cost, including failures and capital, is $5.6 billion[6]. The number of agents in trials for each major class of drugs in each trial phase is listed in the table below.

Table 2

| **Preclinical candidate selection animal testing** | **Phase 1 Safety and pharmacokinetics usually in healthy people** | **Phase 2 target Engaged dose selection AD patients** | **Phase 3 Efficacy in registration** |
|---|---|---|---|
| **Neuropsychiatric agents** | 0 | 6 | 8 |
| **Cognition enhancers** | 2 | 14 | 3 |
| **Disease modifiers** | 28 | 54 | 17 |
| **Total** | 30 | 74 | 28 |
| *Agents with undisclosed mechanisms are not included* | | | |

*Source: Practical Neurology*

# CURRENT PROGRESS

Though Alzheimer's was first identified a century ago, for decades it remained a black box, offering no clues about the mechanics underlying its devastating symptoms. Then, about 40 years ago, scientists discovered beta-amyloid, a protein which they suspected was contributing to brain cell death in Alzheimer's. Once that potential connection was found, investigators had a direction for their work, and funding into researching the disease began in earnest.

Unfortunately, research focused on beta-amyloid has not panned. Many of the late-stage drug trials reporting negative results in recent years have been tests targeting the protein[7]. The silver lining, however, is that much of the knowledge we have gained about other potential treatments has been because of these failures.

While researchers are still trying to understand the role of beta-amyloid in AD, they are also exploring new potential treatment targets ranging from brain inflammation to gut microbiome. Research has revealed that bone marrow stem cells are effective at fighting inflammation and increasing cognition[8]. Our understanding of the role of gut microbiome in Alzheimer's is in its infancy, but, thanks to the early research focused on beta-amyloid, we now know that lipids and other digestive chemicals wind up in the brain, which means they might be manipulated microbially as a treatment approach[9].

Today there are more than a dozen different types of blood markers for AD.

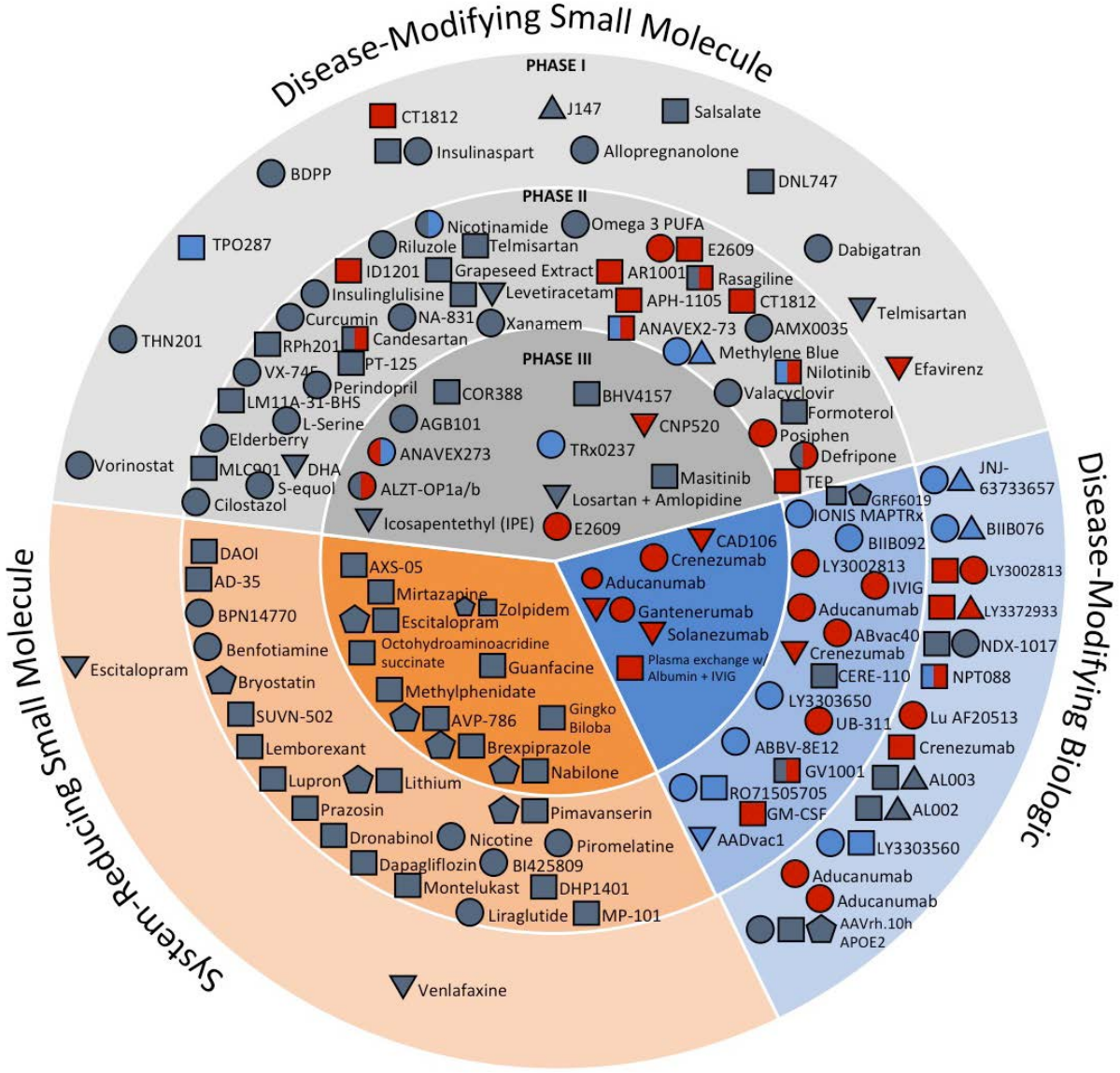
Early research has also has led to new technologies for early diagnosis. While 10 years ago a blood test for Alzheimer's would have been considered wishful thinking, today we have more than a dozen different types of blood markers for Alzheimer's that may be detectable[10]. These are just some of the areas within the vast spectrum of research currently underway.

## THE ALZHEIMER'S DISEASE CLINICAL PIPELINE

As of 2019, there were 132 anti-AD therapies in 156 trials. Figure 1 shows the universe of pharmacologic compounds currently in clinical trials for AD. Nineteen agents (14%) in trials target cognitive enhancement, and 14 (11%) are intended to treat neuropsychiatric and behavioral symptoms. There are 96 agents (73%) that intend to achieve disease modification where 38 (40%) have amyloid, and 17 (18%) have tau as the primary target or as one of several effects seen in nonclinical studies.

One of the hallmarks of Alzheimer's disease is the so-called tau tangles. Tau is a protein contained within the axons of the nerve cells. More specifically, tau helps form microtubules — essential structures that transport nutrients within nerve cells[11].

## 2019 ALZHEIMER'S DRUG DEVELOPMENT PIPELINE Figure 1




*Source: ClinicalTrials.gov*

**SUBJECT CHARACTERISTICS**

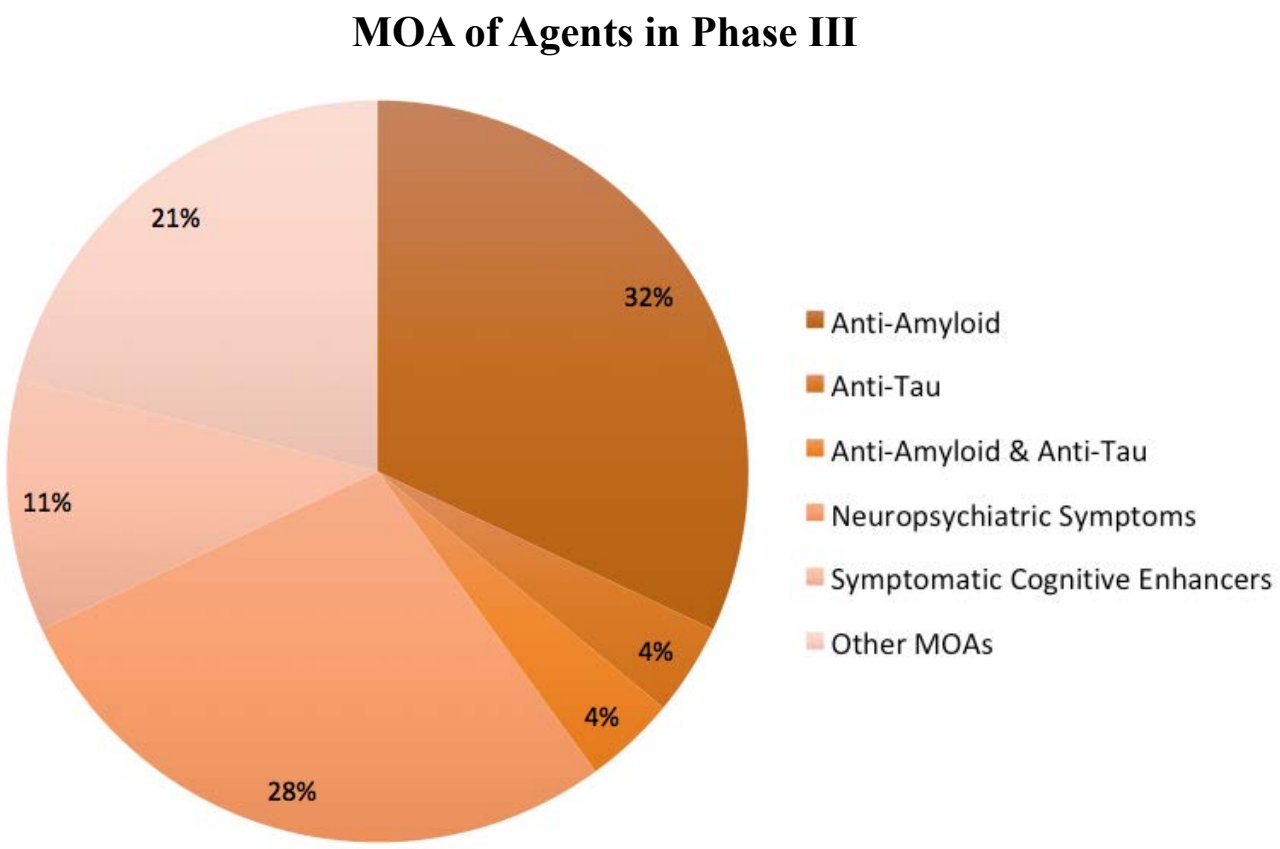
- Healthy Volunteers
- Preclinical
- Prodromal/Prodromal-Mild
- Mild-Moderate
- Severe

**MECHANISMS OF ACTION**

- Amyloid-related
- Tau-related
- Others

Drug discovery and development for AD is arduous. There have been no new drugs approved for almost two decades, and there are no approved disease-modifying treatments (DMTs) for AD. Last year saw a flicker of hope with Biogen's aducanumab after a false call on its failure earlier in the year. On March 2019, Biogen announced it was stopping two studies of aducanumab because an early analysis of the data showed the drug was not likely to provide benefit to people with mild-to-moderate Alzheimer's disease. Then, in October, after taking a more complete review of the data was undertaken, results showed the drug had improved performance on a variety of cognitive tests with the highest dose of aducanumab. Biogen's reexamination of the data must still be subjected to FDA and peer review, and if the results hold up, aducanumab is a step closer in helping slow down patients' cognitive and functional declines.

Other promising agents such as Avanir's AVP-786 and AveXis' AXS-05, which are both in Phase III trials that shows significant improvement on Alzheimer-associated agitation. Drug development continues robustly at all phases despite setbacks in several programs. Experts agree that continuing to pursue therapies for unmet needs require a commitment to growing and accelerating the pipeline[12].



## Alzheimer's Disease Drug Development Agents by Phase Table 3

| PHASE III | | | | | |
|---|---|---|---|---|---|
| **Agent** | **Drug class** | **MOA** | **Sponsor** | **Start date** | **Estimated end date** |
| **Aducanumab** | Anti-amyloid | Monoclonal antibody directed at plaque and oligomers | Biogen | 12/2018 | 11/2025 |
| **CNP520** | Anti-amyloid | BACE inhibitor | Novartis, Amgen, Banner Alzheimer's Institute | 08/2017 | 03/2025 |
| **COR388** | Anti-inflammatory | Bacterial protease inhibitor targeting a periodontal pathogen | Cortexyme | 04/2019 | 12/2022 |
| **Crenezumab** | Anti-amyloid | Monoclonal antibody directed at oligomers | Roche | 03/2016<br>03/2017<br>04/2018 | 07/2021<br>10/2022<br>11/2022 |
| **E2609 (elenbecestat)** | Anti-amyloid | BACE inhibitor | Eisai, Biogen | 10/2016 | 06/2021 |
| **Escitalopram** | Neurotransmitter based | Serotonin reuptake inhibition | NIA, JHSPH Center for Clinical Trials | 01/2018 | 08/2022 |
| **Gantenerumab** | Anti-amyloid | Monoclonal antibody | Roche | 03/2014<br>11/2010<br>06/2018<br>06/2018 | 11/2020<br>08/2020<br>05/2023<br>12/2023 |
| **Gantenerumab & Solanezumab** | Anti-amyloid | Monoclonal antibody directed at plaque and oligomers (gantenerumab) & monoclonal antibody directed at monomers (solanexumab) | Remove amyloid/ reduce amyloid production (DMT) | 12/2012 | 12/2023 |
| **Gingko Biloba** | Metabolic | Plant extract with antioxidant properties | Nanjing Medical University | 08/2016 | 03/2018 |
| **Guanfacine** | Neurotransmitter based | Alpha-2 adrenergic agonist | Imperial College London, UK National Institute of Health Research | 09/2018 | 09/2019 |
| **Icosapent ethyl (IPE)** | Neuroprotective | Purified form of the omega-3 fatty acid EPA | VA Office of Research and Development, University of Wisconsin, Madison | 06/2017 | 11/2021 |
| **Losartan & Amlodipine & Atorvastatin + exercise** | Anti-inflammatory, metabolic | Angiotensin II receptor blocker (Iosartan), calcium channel blocker (amlodipine), cholesterol agent (atorvastatin) | University of Texas Southwestern | 09/2016 | 09/2022 |
| **Masitinib** | Anti-inflammatory | Selective tyrosine kinase inhibitor | AB Science | 01/2012 | 10/2019 |

| PHASE III continued | | | | | |
|---|---|---|---|---|---|
| **Agent** | **Drug class** | **MOA** | **Sponsor** | **Start date** | **Estimated end date** |
| **Methylphenidate** | Neurotransmitter based | Dopamine reuptake inhibitor | Johns Hopkins, NIA | 01/2016 | 08/2020 |
| **Mirtazapine** | Neurotransmitter based | Alpha-1 antagonist | University of Sussex | 01/2017 | 07/2020 |
| **Nabilone** | Neurotransmitter based | Cannabinoid (receptor agent) | Sunnybrook Health Sciences Center | 01/2015 | 03/2019 |
| **Octohydroamino-acridine Succinate Succinate** | Neurotransmitter based | Acetylcholinesterase inhibitor | Shanghai Mental Health Center, Changchun-Huayang High-tech Co, Jiangsu Sheneryang High-tech, Co. | 08/2017 | 02/2020 |
| **Solanezumab** | Anti-amyloid | Monoclonal antibody directed at monomers | Eli Lilly, ATRI | 02/2014 | 07/2022 |
| **TRx0237 (LMTX)** | Anti-tau | Tau protein aggregation inhibitor | TauRx Therapeutics | 01/2018 | 06/2020 |
| **Zolpidem** | Neurotransmitter based | Positive allosteric modulator of GABA-A receptors | Brasilia University Hospital | 10/2016 | 12/2018 |

*Source: ClinicalTrials.gov*
*Abbreviations: ATRI, Alzheimer's Therapeutic Research Institute; BACE, beta-site amyloid precursor protein cleaving enzyme; DMT, disease-modifying therapy; EPA, eicosapentaenoic acid; GABA, gammaaminobutyric acid; GSK, glycogen synthase kinase; NIA, National Institute on Aging; SV2A, synaptic vesicle protein 2A*

| PHASE II | | | | | |
|---|---|---|---|---|---|
| **Agent** | **Drug class** | **MOA** | **Sponsor** | **Start date** | **Estimated end date** |
| **AADvac1** | Anti-tau | Active immunotherapy | Axon Neuroscience | 03/2016 | 06/2019 |
| **ABBV-8E12** | Anti-tau | Monoclonal antibody | AbbVie | 10/2016<br>11/2018 | 09/2022<br>08/2027 |
| **ABvac40** | Anti-amyloid | Active immunotherapy | Araclon Biotech | 02/2018 | 02/2021 |
| **AD-35** | Neurotransmitter based | Acetylcholinesterase inhibitor | Zhejiang Hisun Pharmaceutical, Medspace | 10/2018 | 07/2020 |
| **AMX0035** | Neuroprotective | Blocks mitochondrial and endoplasmic reticulum stress | Amylyx Pharmaceuticals, ADDF, Alzheimer's Association | 08/2018 | 09/2020 |
| **ANAVEX 2-73** | Anti-tau, anti-amyloid, anti-inflammatory | Sigma-1 receptor agonist (high affinity); muscarinic agonist (low affinity); GSK-3b inhibitor | Anavex Life Sciences | 03/2016 | 11/2020 |
| **APH-1105** | Anti-amyloid | Alpha-secretase modulator | Aphios | 06/2021 | 12/2022 |
| **AR1001** | Anti-amyloid | PDE-5 inhibitor | AriBio Co | 01/2019 | 08/2020 |

| PHASE II continued | | | | | |
|---|---|---|---|---|---|
| **Agent** | **Drug class** | **MOA** | **Sponsor** | **Start date** | **Estimated end date** |
| **AstroStem** | Regenerative | Stem cell therapy; autologous adipose tissue derived mesenchymal stem cells | Nature Cell Co | 04/2017 | 07/2019 |
| **BAC** | Undisclosed | Undisclosed | Charsire Biotechnology | 12/2016<br>12/2019 | 11/2019<br>12/2021 |
| **Benfotiamine** | Metabolic | Synthetic thiamine (B1) | Improve multiple cellular processes (cognitive enhancer) | 11/2014 | 11/2019 |
| **B1425809** | Neurotransmitter based | Glycine transporter 1 inhibitor | Boehringer Ingelheim | 08/2016 | 03/2020 |
| **BIIB092** | Anti-tau | Monoclonal antibody | Biogen | 05/2018 | 07/2021 |
| **BPN1477-** | Anti-inflammatory | PDE4D inhibitor | Tetra Discovery Partners | 04/2019 | 06/2020 |
| **Byrostatin** | Metabolic | Protein kinase C modulator | Neurotrope Bioscience | 06/2018 | 07/2019 |
| **Candersartan** | Neuroprotectice, metabolic, anti-amyloid | Angiotensin receptor blocker | Emory University | 06/2016 | 09/2021 |
| **CERE-110** | Neuroprotective, metabolic, anti-amyloid | Angiotensin receptor blocker | Sangamo Therapeutics, ADCS | 09/2009 | 03/2020 |
| **Cilostazol** | Neuroprotective | PDE-3 inhibitor | National Cerebral and Cardiovascular Center, Japan | 07/2015 | 12/2020 |
| **Crenezumab** | Anti-amyloid | Monoclonal antibody targeting soluble oligomers | Genentech, NIA Banner Alzheimer's Institute | 12/2013 | 02/2022 |
| **CT1812** | Anti-amyloid | Sigma-2 receptor antagonist | Cognition Therapeutics | 10/2018<br>04/2018 | 12/2019<br>01/2020 |
| **Curcumin + aerobic yoga** | Neuroprotective | Herb with antioxidant and anti-inflammatory properties | VA Office of Research and Development | 01/2014 | 12/2019 |
| **DAOI** | Neurotransmitter based | NMDA receptor modulation | Chang Chang Memorial Hospital, Taiwan | 05/2015 | 12/2019 |
| **Dapagliflozin** | Metabolic | SGLT2 inhibitor | University of Kansas | 02/2019 | 10/2020 |
| **Deferiprone** | Anti-amyloid, neuroprotective | Iron chelating agent | Neuroscience Trials Australia | 01/2018 | 12/2021 |
| **DHA** | Neuroprotective | Omega-3 fatty acid in high concentration in the brain | University of Southern California | 07/2018 | 09/2024 |
| **DHP1401** | Metabolic | Affects cAMP activity | Daehwa Pharmaceutical Co. | 12/2016 | 06/2019 |
| **Dronabinol** | Neurotransmitter based | CB1 and CB2 endocannabinoid receptor partial agonist | Mclean Hospital, Johns Hopkins University | 03/2017 | 12/2020 |
| **E2609 (elenbecestat)** | Anti-amyloid | BACE inhibitor | Eisai, Biogen | 11/2014 | 06/2020 |

| PHASE II continued | | | | | |
|---|---|---|---|---|---|
| **Agent** | **Drug class** | **MOA** | **Sponsor** | **Start date** | **Estimated end date** |
| **Elderberry juice** | Anti-inflammatory, neuroprotective | Antioxidant rich in anthocyanins | University of Missouri | 09/2016 | 04/2019 |
| **Formoterol** | Metabolic | Beta-2 adrenergic receptor agonist | Palo Alto Veterans Institute for Research, Mylan, Alzheimer's Association | 01/2015 | 07/2018 |
| **Grapeseed extract** | Neuroprotective | Polyphenolic compounds, antioxidant | Mount Sinai School of Medicine, NCCIH | 11/2014 | 09/2018 |
| **GRF6019** | Anti-inflammatory | Human plasma protein fraction infusions | Alkahest | 04/2018<br>12/2018 | 11/2019<br>11/2019 |
| **GV1001** | Anti-amyloid, metabolic | Telomerase reverse transciptase peptide vaccine | GemVax & Kael | 06/2017 | 01/2019 |
| **hUCB-MSCs** | Regenerative | Stem cell therapy | Medipost | 02/2014<br>05/2017<br>10/2017<br>10/2017<br>06/2016 | 07/2019<br>12/2021<br>10/2019<br>10/2019<br>06/2020 |
| **IDI1201** | Anti-amyloid | Alpha-secretase enhancer | IlDong Pharmaceutical | 04/2016 | 12/2018 |
| **Insulin glulisine (intranasal)** | Metabolic | Increase insulin signaling in the brain | HealthPartners Institute | 08/2015 | 05/2019 |
| **IONIS MAPTRx (BIIB080)** | RNA-based anti-tai | MAPT RNA inhibitor antisense oligonucleotide | Ionis Pharmaceuticals, Biogen | 06/2017 | 02/2020 |
| **Lemborexant** | Neurotransmitter based | Dual antagonist of orexin OX1 an OX2 receptors | Eisai, Pursue | 12/2016 | 04/2020 |
| **Levetiracetam** | Neuroprotective | SV2A modulator | University of California San Francisco<br>UCB Pharma | 06/2014<br><br>11/2018 | 12/2019<br><br>01/2020 |
| **Liraglutide** | Metabolic | Glucagon-like peptide 1 receptor agonist | Imperial College London | 01/2014 | 03/2019 |
| **Lithium** | Neurotransmitter based | Ion channel modulator | New York State Psychiatric Institute, NIA | 06/2014 | 04/2019 |
| **LM11A-31-BHS** | Neuroprotective | p75 neurotrophin receptor ligand | PharmatrophiX, NIA | 02/2017 | 10/2019 |
| **Lupron (leuprolide acetate depot)** | Metabolic | Gonadotropin-releasing hormone receptor agonist | New York University | 12/2018 | 12/2020 |
| **L-Serine** | Neuroprotective | Amino acid | Dartmouth-Hitchcock Medical Center, Brain Chemistry Laboratories | 03/2017 | 08/2019 |
| **LY3002813** | Anti-amyloid | Monoclonal antibody | Eli Lilly | 12/2017 | 09/2021 |
| **LY3303560** | Anti-tau | Monoclonal antibody | Eli Lilly | 04/2018 | 10/2021 |
| **Methylene blue** | Anti-tau | Tau protein aggregation inhibitor | Texas Alzheimer's Research and Care Consortium | 07/2015 | 07/2019 |

| PHASE II continued | | | | | |
|---|---|---|---|---|---|
| **Agent** | **Drug class** | **MOA** | **Sponsor** | **Start date** | **Estimated end date** |
| **MLC901 (NeuroAiD)** | Neuroprotective, anti-inflammatory | Traditional Chinese medicine consisting of several herbs | National University Hospital, Singapore | 12/2016 | 06/2019 |
| **Montelukast** | Anti-inflammatory | Leukotriene receptor antagonist | IntelGenx Corp | 11/2018 | 10/2020 |
| **MP-101** | Neurotransmitter based | Enhance mitochondrial functioning | NuroActiva | 09/2018 | 04/2019 |
| **NA-831 (traneurocin)** | Neuroprotective | Undisclosed | Neurogenesis and neuroprotection (DMT) | 09/2018 | 04/2019 |
| **Neflamapimod (VX-745)** | Anti-inflammatory | Selective p38 MAPK inhibitor | EIP Pharma, Toulouse University, Foundation Plan Alzheimer | 10/2018 | 01/2021 |
| **Nicotine** | Neurotransmitter based | Nicotinic acetylcholine receptor agonist | University of Southern California, NIA, ATRI, Vanderbilt University | 01/2017 | 12/2019 |
| **Nilotinib** | Anti-amyloid, anti-tau | Tyrosine kinase inhibitor | Georgetown University | 01/2017 | 12/2019 |
| **Octagam 10%** | Anti-amyloid | 10% human normal immunoglobulin | Sutter Health | 01/2018 | 05/2019 |
| **Omega-3 PUFA** | Neuroprotective | Fish oil concentrate standardized to long chain in n-3 PUFA content | Oregon Health and Science University, NIA | 05/2014 | 09/2019 |
| **Pimavanserin** | Neurotransmitter based | 5-HT2A inverse agonist | Acadia | 02/2017 | 08/2019 |
| **Piromelatine** | Neurotransmitter based | Melatonin receptor agonist; 5-HT 1A and 1D serotonin receptor agonist | Neurim Pharmaceuticals | 11/2015 | 04/2019 |
| **Posiphen** | Anti-amyloid | Selective inhibitor of APP production | QR Pharma, ADCS | 03/2017 | 12/2019 |
| **Prazosin** | Neurotransmitter based | Alpha-1 adrenoreceptor antagonist | ADCS, NIA | 01/2019 | 12/2022 |
| **PTI-125** | Neuroprotective, anti-inflammatory | FLNA inhibitor | Pain Therapeutics, NIH | 11/2018 | 03/2019 |
| **Rasagiline** | Anti-amyloid, neuroprotective, metabolic | Monoamine oxidase B inhibitor | The Cleveland Clinic | 05/2015 | 02/2019 |
| **RO7105705 (MTAU9937 A)** | Anti tau | Monoclonal antibody | Genentech | 10/2017<br>02/2019 | 09/2022<br>09/2021 |
| **RPh201** | Neuroprotective | Undisclosed | Regenera Pharma | 03/2018 | 04/2019 |
| **Sargramostim (GM-CSF)** | Anti-amyloid, neuroprotective | Synthetic granulocyte colony stimulator | University of Colorado, Denver, The Dana Foundation | 03/2011 | 11/2019 |
| **S-equol (AUS-131)** | Neuroprotective | Nonhormonal estrogen receptor B agonist | Ausio Pharmaceuticals | 05/2017 | 10/2019 |
| **SUVN-502** | Neurotransmitter based | 5-HT 6 antagonist | Suven Life Sciences | 09/2015 | 05/2019 |

| PHASE II continued | | | | | |
|---|---|---|---|---|---|
| **Agent** | **Drug class** | **MOA** | **Sponsor** | **Start date** | **Estimated end date** |
| **Telmisartan & Perindopril** | Neuroprotective, anti-inflammatory | Angiotensin II receptor blocker, PPAR-gamma agonist (telmisartan), angiotensin converting enzyme inhibitor (perindopril) | Sunnybrook Health Sciences Center, ADDF | 03/2014 | 03/2021 |
| **TEP** | Anti-amyloid | Antoemetic; activates transport protein ABCCI | Immungenetics AG | 11/2017 | 07/2021 |
| **UB-311** | Anti-amyloid | Active immunotherapy | United Neurosciences | 08/2018 | 03/2021 |
| **Valacyclovir** | Neuroprotective, anti-inflammatory | Antiviral agent | Umea University | 12/2016 | 04/2019 |
| **Xanamem (UE2343)** | Neurprotective | Blocks 11 beta-HSD1 enzyme activity | Actinogen | 03/2017 | 07/2019 |

*Source: ClinicalTrials.gov*
*Abbreviations: ABCC1, ATP binding cassette subfamily C member 1; ADCS, Alzheimer's Disease Cooperative Study; ADDF, Alzheimer's Drug Discovery Foundation; AMPA, a-amino-3-hydroxy-5-methyl4-isoxazolepropionic acid; APOE, apolipoprotein E; APP, amyloid precursor protein; ATRI, Alzheimer's Therapeutic Research Institute; BACE, beta-site amyloid precursor protein cleaving enzyme; cAMP, cycling adenosine monophosphate; CB, cannabinoid; DHA, docosahexaenoic acid; DMT, disease-modifying therapy; FLNA, Filamin A; GM-CSF, granulocyte-macrophage colony-stimulating factor; GSK, glycogen synthase kinase; HSD, hydroxysteroid dehydrogenase; HT, hydroxytriptamine; hUCB-MSCs, human umbilical cord blood derived mesenchymal stem cells; MAPK, mitogen-activated protein kinase; MAPT, microtubule-associated tau; NCCIH, National Center for Complementary and Integrative Health; NIA, National Institute on Aging; NMDA, N-methyl-D-aspartate; PDE, phosphodiesterase; PPAR, peroxisome proliferator-activated receptor; PUFA, polyunsaturated fatty acids; SGLT2, sodium-glucose transporter 2; SV2A, synaptic vesicle protein 2A; TEP, thiethylperazine*

| PHASE I | | | | | |
|---|---|---|---|---|---|
| **Agent** | **Drug class** | **MOA** | **Sponsor** | **Start date** | **Estimated end date** |
| **AAVrh.10hAPOE2** | Neuroprotective | Serotype rh 10 adeno-associated virus gene transfer vector expressing the cDNA coding for human ApoE2 | Cornell University | 01/2019 | 12/2021 |
| **AL002** | Anti-inflammatory | Monoclonal antibody | Alector | 11/2018 | 03/2020 |
| **AL003** | Anti-inflammatory | Monoclonal antibody targeting TREM2 receptor | Alector | 03/2019 | 07/2020 |
| **Allopregnanolone (Allo-IM)** | Neuroprotective, metabolic | GABA receptor modulator | University of Southern California, University of Arizona, Alzheimer's Association | 12/2018 | 12/2020 |
| **BDPP (bioactive dietary polyphenol preparation)** | Neuroprotectice | Combination of grape seed polyphenolic extract and resveratrol | Johns Hopkins University, Mount Sinai School of Medicine | 06/2015 | 10/2019 |

| PHASE I continued | | | | | |
|---|---|---|---|---|---|
| **Agent** | **Drug class** | **MOA** | **Sponsor** | **Start date** | **Estimated end date** |
| **BIIB076** | Anti-tau | Monoclonal antibody | Biogen | 02/2017 | 07/2019 |
| **CKD-355** | Undisclosed | Undisclosed | Chong Kun Dang Pharmaceutical | 02/2019 | 07/2019 |
| **Crenezumab** | Anti-amyloid | Monoclonal antibody targeting oligomers | Genentech | 02/2015 | 09/2023 |
| **CTI812** | Anti-amyloid | Sigma-2 receptor antagonist | Cognition Therapeutics | 05/2018 | 12/2019 |
| **Dabigatran** | Neuroprotective | Direct thrombin inhibitor, anticoagulant | University of Rhode Island, ADDF, Boehringer Ingelheim | 11/2018 | 12/2021 |
| **DNL-747** | Neuroprotective, anti-inflammatory | RIPK1 inhibitor | Denali Therapeutics | 02/2019 | 08/2019 |
| **Efavirenz** | Anti-amyloid | Anti-retroviral; nonnucleoside reverse transcriptase inhibitor | Case Western Reserve University, Cleveland Medical Center, Mass General Hospital | 12/2018 | 05/2020 |
| **Escitalopram & Venlafaxine hMSCs (human mesenchymal stem cells)** | Regenerative | Stem cell therapy | Longeveron | 08/2016 | 03/2020 |
| **Insulin aspart (intranasal)** | Metabolic | Increase insulin signaling in the brain | Wake Forest School of Medicine, NIA, General Electric | 05/2015 | 09/2019 |
| **J147** | Neuroprotective | Mitochondrial ATP synthase inhibitor | Abrexa | 01/2019 | 01/2020 |
| **JNJ-63733657** | Anti-tau | Monoclonal antibody | Janssen | 12/2017 | 10/2019 |
| **Lu AF20513** | Anti-amyloid | Monoclonal antibody | Lundbeck | 03/2015<br>06/2018<br>12/2018 | 12/2019<br>11/2020<br>06/2019 |
| **LY3002813** | Anti-amyloid | Monoclonal antibody | Eli Lilly | 12/2015 | 05/2020 |
| **LY3303560** | Anti-tau | Monoclonal antibody | Eli Lilly | 01/2017 | 06/2020 |
| **LY3372993** | Anti-amyloid | Monoclonal antibody | Eli Lilly | 11/2018 | 09/2021 |
| **MK-4334** | Undisclosed | Undisclosed | Merck | 01/2019 | 06/2019 |
| **NDX-1017** | Regenerative | Hepatocyte growth factor | M3 Biotechnology, ADDF, Biotrial, Inc | 10/2017 | 04/2019 |
| **NPT088** | Anti-amyloid, anti-tau | IgG10Fc-GAIM fusion protein | Proclara Biosciences, Alzheimer's Association | 12/2016 | 04/2019 |
| **Salsalate** | Anti-inflammatory | Nonsteroidal anti-inflammatory | University of California, SF | 07/2017 | 10/2019 |
| **Telmisartan** | Neuroprotective, anti-inflammatory | Angiotensin II receptor blcoker, PPAR-gamma agonist | Emory University | 04/2015 | 04/2019 |
| **THN201** | Neurotransmitter based | Cholinesterase inhibitor + antimalarial glial cell modulator | Theranexus | 09/2018 | 07/2019 |

| PHASE I continued | | | | | |
|---|---|---|---|---|---|
| **Agent** | **Drug class** | **MOA** | **Sponsor** | **Start date** | **Estimated end date** |
| **TPI-287** | Anti-tau | Histone deacetylase inhibitor | German Center for Neurodegenerative Diseases, University Hospital, Bonn, University of Gottingen | 09/2017 | 10/2019 |

*Source: ClinicalTrials.gov*
*Abbreviations: ADDF, Alzheimer's Drug Discovery Foundation; ApoE, apolipoprotein E; BACE, beta-site amyloid precursor protein cleaving enzyme; CSF, cerebrospinal fluid; DMT, disease-modifying therapy; GABA, gamma-aminobutyric acid; GAIM, general amyloid interaction motif; NIA, National Institute on Aging; PPAR, peroxisome proliferator-activated receptor; RIPK1, receptor-interacting serine/threonine-protein kinase 1; SIGLEC-3, sialic acid-binding Ig-like lectin 3; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; TREM2, triggering receptor expressed on myeloid cells 2*

## Add-On Clinical Trials of Combination Treatments for AD Table 4

| Agent | Type | AD Stage | Phase | Baseline Therapy |
|---|---|---|---|---|
| ***DISEASE MODIFYING*** | | | | |
| **Aducanumab** | Amyloid passive immunization | Early | III | SOC |
| **Gantenerumab** | | Early | II/III | NR |
| **Crenezumab** | Amyloid passive immunization | Early | III | SOC |
| **Solanezumab** | Amyloid passive immunization | Early | II/III | NR |
| **JNJ-54861911** | BACE inhibitor | Early | II/III | NR |
| **Masitinib** | Selective tyrosine kinase inhibitor | Mild to Moderate | III | Rivastigmine and/or memantine |
| **ALZT-OPI (cromolyn and ibuprofen)** | Anti-amyloid/anti-inflammatory | Early | III | AChEI's and/or memantine |
| **Flebogama DIF 5% and Albutein 20%** | Intravenous human immunoglobulin, human albumin | Mild to moderate | II/III | AChEI's and/or memantine |
| **BAN2401** | Amyloid passive immunization | Early | II | AChEI's and/or memantine |
| **AADvac-1** | Tau active immunization | Mild | II | AChEI's and/or memantine (permitted but not required) |
| **ABBV-8E12** | Tau passive immunization | Early | II | SOC |
| **Nasal Insulin** | Peptide hormone | Early | II/III | NR, AChEI's and/or memantine |
| **Liraglutide** | GLP-1 receptor agonist | Mild | II | AChEI |
| **Sargramstim** | GM-CSF | Mild to Moderate | II | AChEI's and/or memantine or Axona |
| **Telmisartan** | Angiotensin II receptor antagonist | Mild to Moderate | II | AChEI's and/or memantine |
| **Nicotinamide** | Vitamin B3 | Early | II | SOC |
| **Saracatinib** | Src/abl kinase family inhibitor | Mild | II | AChEI's and/or memantine and/or antidepressants |
| **UE2343** | B-hydroxysteroid dehydrogenase inhibitor | Mild | II | AChEI's and/or memantine |
| **ANAVEX2-73** | Sigma-1 chaperon agonist | Mild to Moderate | II | SOC |
| **BIIB092** | Tau passive immunization | Early | II | SOC |
| **Curcumin and yoga** | Dietary supplement/exercise regimen | MCI | II | NR |

| Agent | Type | AD Stage | Phase | Baseline Therapy |
|---|---|---|---|---|
| **Deep brain stimulation of the fornix** | Procedural intervention | NR | NA | AChEI's and/or memantine |
| **Neflamapimod** | P38 MAPK alpha inhibitor | Early, Mild | II | AChEI's and/or memantine |
| **Repetitive transcranial magnetic stimulation** | Procedural intervention | Mild to Moderate | NA | AChEI |
| **CT1812** | Sigma-2 receptor ligand | Mild to Moderate | I/II | AChEI's and/or memantine |
| **T3D-959** | PPAR&/y agonist | Mild to Moderate | I/II | NR |
| **ACI-24** | Amyloid passive immunization | Mild to Moderate | I/II | AChEI |
| **ACI-35** | Tau active immunization | Mild to Moderate | I | AChEI |
| **ABvac40** | Amyloid active immunization | Mild to Moderate | II | NR |
| **TPI 287** | Microtubule stabilizer | Mild to Moderate | I | SOC |
| **LY3303560** | Tau passive immunization | Early, mild, moderate | NA | AChEI, memantine, and/or other AD therapy |
| **Idalopirdine** | 5-$HT_6$ antagonist | Mild to Moderate | III | Donepezil, AChEI, memantine |
| **Intepirdine** | 5-$HT_6$ antagonist | Mild to Moderate | III | Donepezil |
| **LY3002813** | Amyloid passive immunization | Early | II | AChEI and/or memantine |
| ***SYMPTOMATIC*** | | | | |
| **Levetiracetam** | Anticonvulsant | Mild to Moderate | II | Donepezil, galantamine, rivastigmine, or memantine |
| **SUVN-502** | 5-$HT_6$ antagonist | Moderate | II | Donepezil and memantine |
| **Citalopram** | Selective serotonin reuptake inhibitor | Mild, moderate, severe | III | SOC |
| **Sertraline** | Selective serotonin reuptake inhibitor | NR | II/III | SOC |
| **Risperidone** | Serotonin-dopamine antagonist antipsychotic | NR | IV | NR |
| **Olanzapine** | Multi-acting receptor-targeted antipsychotic | NR | IV | NR |
| **Quetiapine** | Multi-acting receptor-targeted antipsychotic | NR | NA | AChEI |
| **Brexpiprazole** | Partial dopamine receptor agonist | Mild, moderate, severe | II/III | NR |
| **Aripiprazole** | Partial dopamine receptor agonist | Mild, moderate, severe | III | NR |
| **Rasagiline** | Monoamine oxidase B inhibitor | Mild to Moderate | II | AChEI or memantine |
| **Piromelatine** | Melatonin and serotonin receptor agonist | Mild | II | Prescribed drugs for AD including AChEI |
| **Riluzole** | Glutamate neurotransmission modulator | Mild | II | Donepezil or rivastigmine or galantamine |

*Source: Journal of Alzheimer's Disease*
*Abbreviations: 5-HT, 5-hydroxytrytamine (serotonin); AChEI, acetylcholinesterase inhibitor; AD, Alzheimer's disease; BACE, aspartyl protease β-site amyloid precursor protein cleaving enzyme 1; BID, twice-daily; EudraCT, European Clinical Trials Database; GLP-1, glucagon-like peptide-1; GM-CSF, granulocyte-macrophage colony-stimulating factor; IR, immediate release; MAPK, mitogen- activated protein kinase; MCI, mild cognitive impairment; NA, not available; NR, not reported; PPAR, peroxisome proliferator-activated receptor; SOC, standard-of-care medication(s) for AD (agent/dose not specified); XR, extended release.*

## MANAGEMENT OF ALZHEIMER'S DISEASE

Despite the growing population of patients with AD, only five treatment options are currently approved to treat the cognitive symptoms of AD in the United States, the most recent of which (memantine) was approved more than a decade ago. Four of the five standard-of-care treatments are also licensed in the European Union; these include three cholinesterase inhibitors (donepezil[13], galantamine[14], and rivastigmine[15]) and one N-methyl-D-aspartate receptor antagonist (memantine[16]). In 2014, a fifth treatment option consisting of a fixed-dose combination with donepezil and memantine was approved for the treatment of patients with moderate-to-severe AD dementia who are stable on donepezil therapy. Most therapeutic agents under development over the past 15 years have failed; AD is among the least served therapeutic area for drug treatments. Nearly all trials conducted to date have been monotherapy trials comparing an active agent with placebo with or without a background standard-of-care agent, such as cholinesterase inhibitors or memantine.

AD is among the least served therapeutic areas for drug treatments.

There is an increasing appreciation of the complexity of AD, the diversity of pathology, and the dynamic interactive network of components that make up the disease[17]. Several DMTs are currently in clinical studies as add-on therapies to standard of care, cholinesterase inhibitors or memantine, can be found in Table 4.

## CONCLUSION

There are more agents in the AD pipeline in 2019 than were observed in the 2018 pipeline. There are 28 agents in Phase III (2018 had 26), 74 agents in Phase II (2018 had 63), and 30 in Phase I (2018 had 23). While the lack of approval success in the AD drug development may have been historically discouraging, there are a few programs that have successfully demonstrated drug-placebo differences in Phase II and are advancing. Experts agree that progress depends on innovation and learning from exploration of new targets, assessment of new candidates, and implementation of new trial features. As in other chronic diseases such as cancer, HIV, and cardiovascular disease, a learning phase preceded periods of incremental successes that eventually led to meaningful treatments. So, we must forge on.

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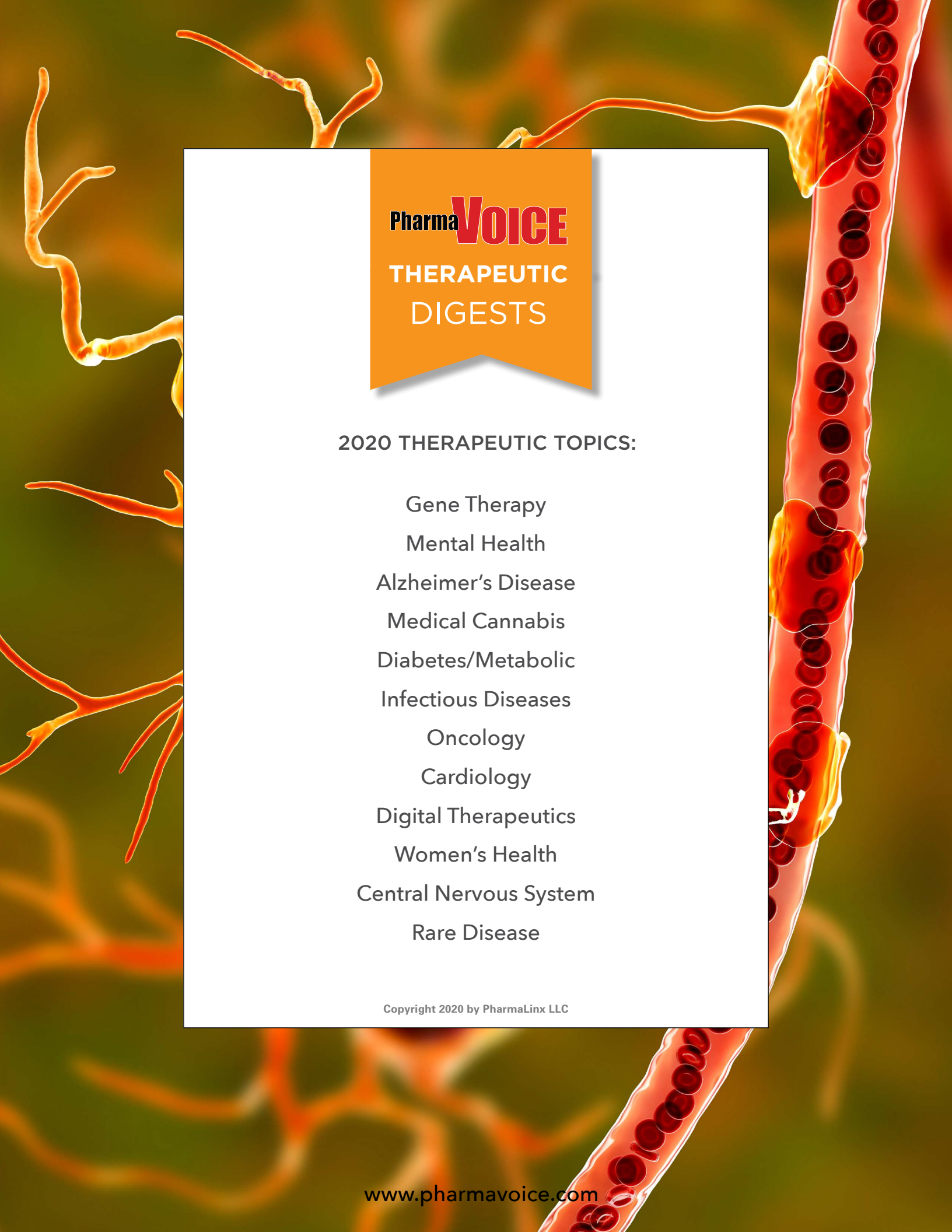

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# THERAPEUTIC DIGESTS

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