Dementia is a syndrome composed of a variety of neurological deficits and impairments that affect memory, problem-solving, and/or language skills, which ultimately impact a patient’s ability to function. Several forms of dementia exist, such as vascular dementia and dementia with Lewy bodies; however, Alzheimer’s disease (AD) is by far the most common, accounting for 50% to 75% of cases. The Centers for Disease Control and Prevention reports AD as the sixth leading cause of death and a major cause of institutionalization; 50% of all nursing home residents have AD or other forms of dementia. With approximately 5.5 million people diagnosed in the U.S., the costs of caring for patients with AD has been estimated at $175 billion, 68% of Medicare and Medicaid’s total costs.

The pathophysiology behind the development of AD is complex and still being researched. One of the leading theories centers on the accumulation of beta-amyloid (Aβ) fibrils that form plaques and lesions within the brain. Destabilization of microtubules resulting in cell death has also been attributed to the creation of neurofibrillary tangles from hyperphosphorylated tau proteins and may represent another disease pathway. Imbalances of neurotransmitters, such as glutamate, acetylcholine, serotonin, and norepinephrine, have also been demonstrated in patients with late stages of AD. Lastly, indirect inflammatory changes from the body’s attempt to clear the Aβ plaques have also been suggested as a potential causative factor. All of these different pathways provide a wealth of potential drug targets.

Currently available treatments for AD come from two main classes of medications: acetylcholinesterase inhibitors (AChEIs) and N-methyl-D-aspartate (NMDA) receptor antagonists. These medications focus on managing neurotransmitter imbalances and can only stabilize a patient’s mental decline; they have not been shown to reverse symptoms of dementia. The role of these medications has been an area of debate given their associated costs, minimal therapeutic effects, and adverse effects, such as gastrointestinal issues, dizziness, or headache. A summary of these medications can be found in Table 1.

The pharmaceutical industry has focused intensely on developing new treatments for AD, but it has been met with many setbacks over the past several years. Failures of major clinical trials have been seen with various therapeutic classes. In November 2016, Eli Lilly announced its monoclonal antibody (mAb) candidate solanezumab failed to meet its primary endpoint in the large phase 3 EXPEDITION-3 trial, and the company will not pursue the drug’s approval for treating mild AD. Prior to that, Pfizer’s bapineuzumab also failed in two phase 3 trials, which led that company to terminate all other ongoing studies. In September 2017, Axovant released negative topline results from its phase 3 trial evaluating intepirdine, a small-molecule therapy, and subsequently abandoned further development of this agent. This pattern highlights the complexity of this disease state, the difficulties associated with appropriate patient selection, and the appropriate timing of therapy.

Despite this precedent, the pipeline of medications aiming to treat AD is robust as each company hopes to be the first to bring an effective therapy to market. Clinical trials are focusing both on treating the progression of AD and managing the symptoms associated with advanced dementia, such as agitation. Medications targeting AD management can be categorized as either small-molecule drugs or as larger, protein-based therapies. The following is a discussion, in no particular order, of several upcoming medications that are in late-phase development for AD.

**Gantenerumab**

Roche has two potential biological products coming to market—gantenerumab and crenezumab. Gantenerumab is a fully humanized mAb that works against Aβ fibrils in the brain and facilitates their clearance through cell-mediated responses. Clinical findings with gantenerumab have been mixed, and the SCARLET ROAD trial, which evaluated 797 patients with prodromal AD, was discontinued due to futility in its primary endpoint of change in clinical dementia rating (CDR). However, the trial suggested potential benefit in a subgroup analysis for patients who were likely to be fast progressors and received higher doses. Another phase 3 trial, MARGURITE ROAD, that was evaluating patients with mild disease has stopped recruiting patients and is continuing to monitor outcomes with no results yet reported. Based on the subgroup findings, additional phase 3 trials (GRADUATE 1 and 2) are being planned to evaluate higher doses of gantenerumab in patients with prodromal to mild AD.

Treatment with gantenerumab was associated with an increase in amyloid-related imaging abnormalities (ARIA), such as encephalopathy (ARIA-E) and hemosiderin deposition (ARIA-H). These abnormalities can be seen with all amyloid-targeting mAbs. ARIA-E is associated with edema, typically developing in the parietal, occipital, or frontal lobes, which can be asymptomatic or result in confusion or altered mental status. ARIA-H is thought to come from deposits of iron in the form of hemosiderin in the brain as a result of a small leakage of blood into adjacent tissue. The development of these adverse effects may present problems in future trials that are evaluating higher doses of gantenerumab because the incidence of ARIA-E appeared to be dose-dependent with rates of 0.8%, 6.6%, and 12.3% in the placebo, 105-mg, and 225-mg groups, respectively. ARIA-H occurred with a frequency of 10.9%, 19.2%, and 13.1% in...
the placebo, 105-mg, and 225-mg groups, respectively.14

Crenezumab

Crenezumab is an mAb with affinity for multiple aggregated forms of Aβ as well as monomers and oligomers, and it is hypothesized that crenezumab’s ability to bind multiple forms of Aβ provides a lower risk for patients developing ARIA-E. Results from the phase 2 ABBY and BLAZE trials provided divergent results. ABBY evaluated 431 patients with mild-to-moderate AD who received differing doses of crenezumab every two or four weeks. This trial failed to demonstrate any significant reduction in the Alzheimer’s Disease Assessment Scale–Cognitive 12 (ADAS-cog12) or CDR-Sum of Boxes (CDR-SOB), which was the primary endpoint. An exploratory analysis of patients with only mild disease suggested a possible benefit in ADAS-cog12 decline (35% reduction; \( P = 0.036 \)) but not in CDR–SOB (19% reduction; \( P = 0.42 \)).15 The BLAZE trial evaluated changes in biomarkers such as Aβ levels in the brain and cerebrospinal fluid (CSF). This trial also failed to meet its primary endpoint of Aβ levels in the brain, but was able to produce slight but significant increases in CSF concentrations, which are suggestive that crenezumab is interacting with brain plaques.16 Initial safety data suggest crenezumab is well tolerated with no reports of ARIA-E in a dose-escalation study conducted in 52 patients. There were six cases of ARIA-H, but they did not require discontinuation of the medication.11

Based on the data from these phase 2 trials, Roche is moving forward with two phase 3 clinical trials. CREAD1 and CREAD2 are ongoing studies of 60 mg/kg intravenous (IV) crenezumab every four weeks versus placebo to evaluate the efficacy in patients with prodromal to mild AD. The estimated completion date is 2022 for these trials.17 It will be important to see if crenezumab is able to maintain its initial safety profile in these larger clinical trials.

Aducanumab

Aducanumab is a recombinant human mAb derived from natural Aβ-specific antibodies. As a treatment, it is reported to bind to oligomers and insoluble fibrils of Aβ but not monomers. The ongoing phase 1b PRIME study was designed to evaluate the pharmacokinetics and pharmacodynamics of multiple doses of aducanumab while also evaluating Aβ plaque formations in the brain. Results from a 36-month follow-up were released in August 2017 that showed that amyloid plaques decreased in a time- and dose-dependent manner almost to the point of nondetection as demonstrated through positron emission topography scans. Results also suggested benefit in the patients’ rate of decline in CDR–SOB and Mini-Mental Status Exam scores.

### Table 1 Current FDA-Approved Medications for Alzheimer’s Disease Treatment11,37

<table>
<thead>
<tr>
<th>Drug Manufacturer</th>
<th>Mechanism</th>
<th>Approved Use</th>
<th>Formulations</th>
<th>Dosing</th>
<th>AWP37 (30-Day Supply at Maximum Dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aricept (donepezil)</td>
<td>AChEI</td>
<td>Mild to severe AD</td>
<td>IR: 5-mg, 10-mg, and 23-mg tablets</td>
<td>Mild AD: 5–10 mg once daily</td>
<td>IR: $607</td>
</tr>
<tr>
<td>Eisai, Inc.</td>
<td></td>
<td></td>
<td>ODT: 5-mg and 10-mg tablets</td>
<td>Severe AD: 10–23 mg once daily</td>
<td>ODT: N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IR: $312</td>
<td>ODT: $210</td>
</tr>
<tr>
<td>Razadyne (galantamine)</td>
<td>AChEI</td>
<td>Mild to moderate AD</td>
<td>IR: 4-mg, 8-mg, and 12-mg tablets</td>
<td>IR: 8–12 mg twice daily</td>
<td>IR or ER: $384</td>
</tr>
<tr>
<td>Janssen</td>
<td></td>
<td></td>
<td>ER: 8-mg, 16-mg, and 24-mg tablets</td>
<td>ER: 8–24 mg once daily</td>
<td>OS: N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OS: 4 mg/mL</td>
<td>OS: 8–12 mg twice daily</td>
<td>IR: $127</td>
</tr>
<tr>
<td>Exelon (rivastigmine)</td>
<td>AChEI</td>
<td>IR: mild to moderate AD</td>
<td>IR: 1.5-mg, 4.5-mg, and 6-mg capsules</td>
<td>IR: 3–6 mg twice daily</td>
<td>IR: $413</td>
</tr>
<tr>
<td>Novartis</td>
<td></td>
<td>TD: severe AD</td>
<td>TD: 9.5-mg and 13.3-mg patches</td>
<td>TD: 9.5–13.3 mg once daily</td>
<td>TD: $777</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TD: $486</td>
</tr>
<tr>
<td>Namenda (memantine)</td>
<td>NMDA receptor antagonist</td>
<td>Moderate to AD</td>
<td>IR: 5-mg and 10-mg tablets</td>
<td>IR and OS: 10 mg twice daily</td>
<td>IR: $534</td>
</tr>
<tr>
<td>Allergan</td>
<td></td>
<td>TD: severe AD</td>
<td>ER: 7-mg, 14-mg, and 28-mg capsules</td>
<td>ER: 28 mg once daily</td>
<td>ER: $509</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OS: 2 mg/mL</td>
<td>OS: $1,032</td>
<td>OS: N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OS: $635</td>
</tr>
<tr>
<td>Namzaric (memantine/donepezil)</td>
<td>Combination AChEI and NMDA receptor antagonist</td>
<td>Moderate to severe AD</td>
<td>ER: 7 mg/10 mg, 14 mg/10 mg, 21 mg/10 mg, and 28 mg/10 mg capsules</td>
<td>28 mg/10 mg once daily</td>
<td>$507</td>
</tr>
<tr>
<td>Allergan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
</tbody>
</table>

*AWP for lowest-price generic drug at the time of writing.

AChEI = acetylcholinesterase inhibitor; AD = Alzheimer’s disease; AWP = average wholesale price; ER = extended release; IR = immediate release; N/A = not available; NMDA = N-methyl-D-aspartate; ODT = orally disintegrating tablet; OS = oral solution; TD = transdermal.
While these data are encouraging, it must be noted that these findings are based on 143 patients, and there were reports of ARIA-E in 46 patients, though this mostly did not result in discontinuation of the drug.18 These reports have generated a lot of excitement from key opinion leaders, but some remain skeptical until further safety and cognitive efficacy data are reported.

Biogen and Neurimmune are conducting two phase 3 trials, ENGAGE and EMERGE, to evaluate the role of long-term plasmapheresis with Flebogamma/Albutein. The rationale behind this approach stems from observational studies showing that IVIG may contain antibodies against Aβ and thus may have a role in disease treatment or prevention. Data have been conflicting. Retrospective analyses have suggested a reduced risk of AD in patients receiving IVIG for other indications, but phase 2 or 3 trials were unable to demonstrate an impact in patients with mild-to-moderate AD.20 Reasons for these discrepancies include the various doses of IVIG studied, the timing of treatment initiation, and the formulations of IVIG used. The AMBAR trial is evaluating the role of long-term plasmapheresis with Flebogamma/Albutein following an initial plasma exchange procedure. The trial has finished enrolling patients, but preliminary results have not been released.21 Concerns about this treatment method include the patient inconvenience of requiring regular plasmapheresis, need for specialized staff and equipment at facilities, and maintaining a sufficient supply of IVIG, a human-derived product.

**Verubecestat**

Another potential target for small molecules is the beta-secretase 1 cleaving enzyme (BACE), a key enzyme in initiating the formation of Aβ plaques in the brain.22 Medications in this class would be used as preventive therapy for preclinical patients or for those with early stages of AD. Verubecestat is a BACE inhibitor that demonstrated the ability to produce a greater than 90% reduction of Aβ plaques in the CSF of healthy volunteers in three phase 1 trials. Following these initial successes, Merck proceeded with two phase 3 trials, EPOCH and APECS, which evaluated patients with mild-to-moderate AD and

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**Table 2 Therapies for Alzheimer’s Disease Currently in Late-Stage Development**11

<table>
<thead>
<tr>
<th>Medication Developer(s)</th>
<th>Mechanism of Action</th>
<th>Targeted Indication</th>
<th>Route and Dose</th>
<th>Expected Price Strategy</th>
<th>Anticipated U.S. Launch Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gantenerumab Roche/MorphoSys</td>
<td>Anti-Aβ mAB</td>
<td>Prodromal to mild AD</td>
<td>Subcutaneous injection, dose TBD</td>
<td>Priced in reference to aducanumab</td>
<td>2021</td>
</tr>
<tr>
<td>Crenzumab Roche/Genentech</td>
<td>Anti-Aβ mAB</td>
<td>Prodromal to mild AD</td>
<td>IV, 60 mg/kg or 180 mg/kg every four weeks</td>
<td>Priced in reference to gantenerumab</td>
<td>2023</td>
</tr>
<tr>
<td>Aducanumab Neurimmune/ Biogen</td>
<td>Anti-Aβ mAB</td>
<td>Prodromal to mild AD</td>
<td>IV, 3 mg/kg, 6 mg/kg, or 10 mg/kg every four weeks</td>
<td>Anticipated to be priced significantly above current AD therapy; likely to have first-to-market advantage</td>
<td>2020</td>
</tr>
<tr>
<td>Flebogamma/ Albutein Grifols Biologicals</td>
<td>IVIG–albumin combination</td>
<td>Mild to moderate AD</td>
<td>IV, with plasmapheresis, dose TBD</td>
<td>Anticipated costs would be much higher than other therapies given the manufacturing process and procedures needed</td>
<td>2023</td>
</tr>
<tr>
<td>Verubecestat Merck</td>
<td>BACE inhibitor</td>
<td>Prodromal AD</td>
<td>Oral, 12 mg or 40 mg once daily</td>
<td>Expected to be priced higher than current therapies, but similar to other in-class medications</td>
<td>2020</td>
</tr>
<tr>
<td>Elenbecestat Eisai/Biogen</td>
<td>BACE inhibitor</td>
<td>Prodromal to moderate AD</td>
<td>Oral, 50 mg once daily</td>
<td>Expected to be priced higher than current therapies, but similar to other in-class medications</td>
<td>2021</td>
</tr>
<tr>
<td>Lanabecestat AstraZeneca/ Eli Lilly</td>
<td>BACE inhibitor</td>
<td>Prodromal to mild AD</td>
<td>Oral, 20 mg or 50 mg once daily</td>
<td>Expected to be priced higher than current therapies, but similar to other in-class medications</td>
<td>2020</td>
</tr>
<tr>
<td>Azeliragon vTv Therapeutics</td>
<td>RAGE inhibitor</td>
<td>Mild AD</td>
<td>Oral, 5 mg once daily</td>
<td>Expected to be priced at a large premium over currently available small-molecule therapies</td>
<td>2020</td>
</tr>
<tr>
<td>Nilvadipine Archer Pharmaceuticals</td>
<td>Dihydropyridine calcium-channel antagonist</td>
<td>Mild to moderate AD</td>
<td>Oral, 8 mg once daily</td>
<td>Expected to be priced above current small-molecule therapies, but lower than immunotherapies</td>
<td>2018</td>
</tr>
</tbody>
</table>

AD = Alzheimer’s disease; anti-Aβ mAB = anti-amyloid-beta monoclonal antibody; BACE = beta-secretase; IV = intravenously; IVIG = intravenous immune globulin; RAGE = receptor for advanced glycation end products; TBD = to be determined.
prodromal AD, respectively. However, in February 2017, Merck terminated the EPOCH study after an interim analysis concluded there was no chance of finding a positive clinical effect.\textsuperscript{23} The APECS trial was discontinued in February 2018 after an external data monitoring committee concluded that it was unlikely that positive benefit/risk could be established if the trial continued.\textsuperscript{24}

**Lanabecestat**

AstraZeneca and Eli Lilly are co-developing lanabecestat, also a BACE inhibitor, for the treatment of AD. Following extensive phase 1 trials, lanabecestat was shown to reduce CSF concentrations of Aβ in a dose-dependent manner. Larger studies, such as the phase 3 DAYBREAK and phase 2/3 AMARANTH trials, are currently under way to evaluate the use of lanabecestat in patients with early AD with anticipated end dates of 2021 and 2019, respectively.\textsuperscript{25,26} Data from phase 1 studies demonstrated a 76% or greater reduction in CSF Aβ levels following multiple doses of 50 mg daily with no major safety concerns observed in the small sample sizes.\textsuperscript{27}

**Elenbecestat**

A third BACE inhibitor, elenbecestat, is being developed by Eisai and Biogen. Similar to the other agents in this class, elenbecestat has demonstrated the ability to substantially reduce concentrations of Aβ in the CSF and was well tolerated with only mild adverse effects of headache and dizziness. Two phase 3 trials are under way, MISSION AD1 and MISSION AD2, that are evaluating 50 mg elenbecestat once daily in more than 1,300 patients with prodromal AD or early mild AD with a projected completion in late 2020.\textsuperscript{28}

**Future BACE Inhibitors**

Two additional BACE inhibitors are also in development, but on longer timelines than previously mentioned agents.

Janssen and Shionogi are developing JNJ-54861911 for the treatment of asymptomatic patients who are at risk of developing AD. This BACE inhibitor is being evaluated in the phase 2/3 EARLY trial, but because the primary outcome is prevention of disease, the trial will last longer than other ongoing trials and is expected to be complete in 2023.\textsuperscript{29}

Novartis is developing CNP520 for the prevention of AD in patients determined to be high risk based on their age, apolipoprotein E genotype, and presence of elevated amyloid levels. One trial, GENERATION S2, is comparing CNP520 with placebo in these high-risk patients.\textsuperscript{30} The other trial, GENERATION S1, is being conducted in collaboration with Amgen to evaluate CNP520 and Amgen’s CAD106 immunotherapy to assess the impact of these different therapies on preventing the onset of AD. It is anticipated that CNP520 would not launch until 2025.\textsuperscript{31}

A proposed future role for the BACE inhibitor class is use in combination with immunotherapy treatments; however, large-scale clinical studies would need to be conducted to justify this therapeutic combination.

**Azeliragon**

Azeliragon (vTv Therapeutics) is in development to inhibi the receptor for advanced glycation end products (RAGE) pathway to treat AD. The stimulation of RAGE by Aβ has been observed to drive amyloid plaque formation. A phase 3, placebo-controlled trial, STEADFAST, is evaluating azeliragon 5 mg daily in combination with an AChEI with or without memantine in 800 patients with mild AD and is expected to be completed in 2018.\textsuperscript{32} A phase 2 trial that compared higher doses of 20 mg azeliragon per day with 5 mg per day and placebo found higher rates of confusion (8.1% versus 4.5%) and falls (10.3% versus 6.1%) as well as greater cognitive decline in the 20-mg group compared with the placebo group.\textsuperscript{11}

**Nilvadipine**

The dihydropyridine calcium-channel blocker nilvadipine is under evaluation by Archer Pharmaceuticals. Nilvadipine helps to maintain calcium homeostasis within the brain and promotes clearance of soluble amyloid peptides to prevent their deposition into plaques. A large phase 3 trial evaluating 511 participants across nine European countries was completed in December 2016, but results are still pending publication.\textsuperscript{33} In a small safety analysis in 86 patients with AD (56 received nilvadipine and 30 received placebo), the development of orthostatic hypotension was seen in 84% of patients in the treatment arm.\textsuperscript{34} This safety aspect may be of concern given the increased risk of falls present in elderly patients with dementia.

**Intepirdine**

Axovant Sciences’ candidate intepirdine, an antagonist of serotonin receptor 6 (5-HT₆), was being evaluated in the treatment of mild-to-moderate AD in the MINDESET study. Results from this trial showed no difference between intepirdine and placebo in the patients’ ADAS-cog or ADAS-Activities of Daily Living scores.\textsuperscript{9} Axovant will continue to evaluate other doses of intepirdine in the treatment of other diseases, such as dementia with Lewy bodies. The outcome of the MINDESET trial was similar to previous results for other medications in this class. Idalopirdine was a candidate that produced promising phase 2 results but subsequently had negative results in three phase 3 trials. Pfizer discontinued its candidate, PF-05212377, after a phase 2 trial determined futility.\textsuperscript{35,36} This string of failures suggests that this may not be a viable therapeutic class in AD.

Older medications, such as pioglitazone and the combination of cromolyn plus ibuprofen, are being evaluated for their impact on modifying AD, but expectations are low for these therapies to have a major impact or gain much market share.\textsuperscript{11}

Other clinical trials are evaluating medications to manage symptoms associated with AD. Brexpiprazole (Rexulti, Otsuka America Pharmaceutical, Inc.) and aripiprazole are two currently approved medications being evaluated for the management of agitation in AD and would be expected to enter the market for this indication in 2018 and 2019, respectively. Novel agents for the management of agitation include Avanir/Otsuka’s AVP-786, a modified formulation of the current medication dextromethorphan hydrobromide/quinidine sulfate (Nuedexta, Avanir) and Intracelluar Therapies’ lumateperone tosylate, a 5-HT₂A receptor antagonist.\textsuperscript{11} These therapies may prove beneficial, but they may struggle to gain market share because they would likely enter behind brexpiprazole and aripiprazole.

**CONCLUSION**

The pipeline for AD is filled with many potential candidates from varying therapeutic classes. While the prospect
of finding a viable treatment is exciting, practitioners will likely be skeptical until robust clinical trial data are available given the recent history of initial promise but ultimate disappointment with several agents.

REFERENCES


