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Drug Development for Alzheimer's Disease: Where Are We Now and Where Are We Headed?

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Abstract

Objective—To provide a brief survey of the clinical development of Alzheimer's disease (AD) pharmacotherapy.

Methods—The search process included PubMed, www.ClinicalTrials.gov, the International Conference on Alzheimer's Disease 2008 (ICAD), and pharmaceutical company and AD advocacy Web sites. Selected articles were primary manuscripts reporting clinical trial or preclinical study results in English in peer-reviewed journals.

Results—The AD pipeline comprises a large number of drugs with differing targets and mechanisms of action. No novel agent, since the approval of memantine in 2002, has successfully completed a phase 3 trial however, encouraging phase 2 results were reported for several compounds at ICAD 2008, and the overall number and variety of novel agents in clinical development continues to expand.

Conclusions—Despite clearly disappointing results of recently completed phase 3 trials for several leading novel compounds, the breadth and depth of the clinical development pipeline at all phases of development provides ample justification to expect that new pharmacotherapeutic options will become available for the treatment of AD within the next 3 to 5 years. Nonetheless, it is not yet clear which agent or therapeutic strategy will be the next to be approved for clinical use. In the meantime, it is important to not underestimate the value of currently available treatments, and to ensure that every patient with AD is prescribed optimal pharmacotherapy as early in the course of the disease as possible.

INTRODUCTION

The cholinesterase inhibitors (ChEIs) and memantine have been revolutionary in changing Alzheimer's disease (AD) from a disease for which there was no effective pharmacotherapy to a disease for which there is treatment. These agents provide detectable symptomatic improvement and have a modest impact on the progression of the disease from mild cognitive impairment (MCI) to disabling dementia and death.[1,2] Nonetheless, the therapeutic limitations of ChEIs, as well as the steadily increasing prevalence of the disease, have led to increased basic and clinical research aimed at developing better medications for the treatment of AD. Several drugs with widely differing targets are currently in development, some discovered serendipitously, some designed rationally based on evolving knowledge of the pathophysiology of AD, and some identified from epidemiologic research. To date, however, no novel agent has successfully cleared the gauntlet of all phases of the clinical development process.

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The purpose of this article is to provide an overview for the practicing neurologist, geriatrician, psychiatrist, or primary care physician of the state of clinical development of AD pharmacotherapy at the beginning of 2009. The discussion begins by describing the recent history of compounds that have failed to demonstrate sufficient efficacy to gain regulatory approval. Unfortunately, that group comprises every drug that has completed phase 3 trials since the approval of memantine in 2002. Fortunately, the pipeline is so robust and varied that the number of these disappointing agents is eclipsed by the much greater number of compounds currently in clinical development.

Although the focus of the discussion is on the clinical trials themselves, the putative mechanism of action of each therapeutic agent is also described. Because it is highly unlikely that any of these individual agents will provide a cure for AD, the future treatment of AD is likely to involve polypharmacy, with newer medications given in combination with ChEIs and with each other. Indeed, with the addition of memantine, polypharmacy for AD treatment has already begun.

METHODS

All source material was obtained from the public record; no proprietary information or private opinions were sought. The search process included:

- PubMed searched using the keywords “Alzheimer's disease” AND “clinical trials” for years 2003–2008; “dementia” AND “prevention” AND “clinical trials” for years 2003–2008; and the chemical name of every compound mentioned in any article on new drugs for AD since 2005.
- www.ClinicalTrials.gov searched using the keyword “Alzheimer's disease.”
- International Conference on Alzheimer's Disease (ICAD) 2008, all abstracts searched for reports of clinical trial results.
- The Internet was searched using Google; keywords used were the chemical and brand names (where applicable) of each agent. Web sites of pharmaceutical companies and AD advocacy groups were also searched internally using each compound's generic name and/or company designation.
- Inclusion/Exclusion criteria: articles had to be primary manuscripts reporting the results of a clinical trial or peer-reviewed articles on preclinical studies. Internet sources were restricted to official trial registries, official pharmaceutical company sites, mainstream AD organization sites, and AD congress sites. Opinion was excluded; only specific details of actual trials, conducted or planned, were included.
- Clinical trials included: all trials used a randomized, double-blind, placebo-controlled, parallel-group group design.

COMPLETED PHASE 3 TRIALS (Table I)

(Note: Agents in this and subsequent sections are presented in alphabetical order to maintain neutrality and fair balance.)

Ginkgo Biloba

Ginkgo biloba is widely used as an unconventional herbal treatment for the prevention and treatment of aging-associated cognitive decline, including AD.[3] As part of the National Institute of Health's complementary medicine initiative, a clinical trial was conducted at 5 US academic centers between the years 2000 and 2008 comparing an extract of *G biloba* (120 mg twice daily [bid]) with placebo in 3069 elderly community-dwelling volunteers (normal

cognition, n = 2587; amnestic MCI [aMCI], n = 482). Participants were evaluated every 6 months and the primary outcome measures were incident dementia and AD (determined by expert panel consensus). The results showed no effect of *G biloba* on the progression to AD (hazard ratio [HR], 1.16; 95% confidence interval [CI], 0.97–1.39; $P = 0.11$) or all-cause dementia (HR, 1.12; 95% CI, 0.94–1.33; $P = 0.21$). A subset analysis of participants with aMCI at baseline was similar (HR, 1.13; 95% CI, 0.85–1.50; $P = 0.39$). Overall, a nonsignificantly greater number of subjects treated with *G biloba* developed dementia (n = 277; 3.3 per 100 person-years) compared with placebo (n = 246; 2.9 per 100 person-years). This study provides strong evidence that *G biloba* does not have a role in the prevention of AD.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

There is a large and diverse body of evidence suggesting that NSAIDs could be effective for the treatment, and especially for the prevention, of AD. Epidemiologic studies suggest that nonaspirin NSAIDs commonly used by the elderly for relief of pain or inflammatory conditions may protect against the development of AD.[4,5] These studies are supported by cell culture and animal experiments showing that NSAIDs reduce brain inflammatory markers such as activated microglia,[6,7] and may reduce brain deposits of amyloid-β (Aβ) peptide.[8,9] Further, certain NSAIDs have been shown in laboratory experiments to selectively lower the more pathogenic Aβ42 species compared with the reportedly more benign Aβ40, suggesting a subtle alteration in γ-secretase activity. At least 4 prospective studies have investigated the relationship between NSAID use and AD, with results that generally support the notion that NSAIDs reduce the risk of incident AD.[10-13] Two of these studies suggest that longer duration of use confers greater risk reduction[10,12]; however, randomized clinical trials in patients with AD or in populations at high risk of the disorder have failed to indicate that NSAIDs are effective treatments for patients with established AD[14-16] or MCI.[17] In addition, the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT), the first prospective primary prevention trial exploring naproxen and celecoxib treatment applied to at-risk subjects, failed to demonstrate a protective benefit against conversion to AD or cognitive decline after 2 years of observation.[18] After 5 years of observation, a protective benefit in the naproxen group vs celecoxib or placebo was found, but this benefit may be offset by higher morbidity and mortality in that group.[19]

Phenserine

In addition to being a selective ChEI, phenserine has also been shown in animal studies to inhibit the formation of Aβ, thus conferring 2 potential mechanisms of action in the treatment of AD.[20] A 6-month, pivotal phase 3 trial enrolled 384 patients with mild to moderate AD and randomized participants to receive phenserine 10 mg or 15 mg or placebo bid. Although phenserine-treated patients performed better on the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) and the Clinician's Interview-Based Impression of Change (CIBIC), the primary outcome measures, the results were not significant and the AD clinical development program was terminated.[21] A phase 2b study involving 20 patients did, however, provide the first evidence in humans that phenserine reduces cerebrospinal fluid (CSF) levels of Aβ as well as the formation of amyloid plaques as demonstrated by cortical Pittsburgh Compound B retention.[22] This encouraging finding has led to efforts to develop the levo-isomer of phenserine, called posiphen.[23]

Statins (Simvastatin and Atorvastatin)

Elevated midlife cholesterol levels are associated with an increased risk of AD,[24] and the use of statins chronically reduces the risk for developing AD by up to 75%.[25] There are also robust scientific data demonstrating that hypercholesterolemia promotes Aβ production and deposition in a variety of animal models of AD and that cholesterol reduction strategies reduce

Aβ deposition. A 6-month study found that probucol, a cholesterol-lowering drug, reduced levels of Aβ in CSF and stabilized cognitive deterioration in patients with mild to moderate AD[26]; however, in short-term studies, statins have demonstrated limited ability to reduce Aβ.[27] In addition, although a phase 2 study of atorvastatin monotherapy in patients with mild to moderate AD found that the treated group showed no deterioration in cognitive and functional assessment scales after 12 months of treatment,[28] a larger phase 3 study in 600 patients also receiving donepezil, completed in 2007, showed no benefit of adjunctive atorvastatin.[29] A phase 3 trial (N = 400) of simvastatin monotherapy, also completed in 2007, was also negative.[30]

Nonetheless, the epidemiologic data suggesting a protective effect of statins, as opposed to a treatment effect, is sufficiently encouraging[31] that simvastatin is now in a phase 2 trial to assess its potential as a preventive agent.[32] This study will enroll 100 adults, aged 35–69, who have a parent with AD but who do exhibit any cognitive deficits. The primary outcome measures include CSF Aβ, inflammatory markers, and cholesterol, as well as memory and thinking skills, and there is also a magnetic resonance imaging (MRI) substudy.

Tarenflurbil

Amyloid precursor protein (APP) is cleaved by γ-secretase to form Aβ42, and it has therefore been hypothesized that selective Aβ42-lowering agents (SALAs) should be useful in the treatment or prevention of AD.[33,34] Tarenflurbil, the R-enantiomer of the NSAID flurbiprofen, was the first γ-secretase modulator to reach the final stage of clinical development. Results of an earlier phase 2 trial in 210 patients had shown beneficial effects of tarenflurbil 800 mg bid in patients with mild AD on measures of daily activities and global function.[35] The 18-month, phase 3 trial (N = 1600), conducted in 133 US sites, examined the effect of tarenflurbil 800 mg tid in patients with mild AD (mean Mini-Mental State Examination [MMSE], 23), 81% of whom were on stable dosages of a ChEI, memantine, or a combination.[36] The primary outcome measures were the ADAS-cog and the ADAS-activities of daily living scale (ADAS-ADL), assessed every 3 months. There was no difference between placebo- and tarenflurbil-treated patients; at study end point both groups had lost an average of 7 points on the ADAS-cog and 10 points on the ADAS-ADL. Ironically, the observation of this magnitude of decline over 18 months in patients with mild AD, the majority of whom were receiving conventional medical treatment, confirms that adequately powered clinical trials of this duration should be able to detect an efficacy signal. One speculative explanation for tarenflurbil's lack of efficacy is inadequate central nervous system (CNS) penetration.

Tramiprosate

Tramiprosate, a modification of the amino acid taurine that functions as a glycosaminoglycan mimetic, was designed to cross the blood-brain barrier and bind soluble Aβ peptides in order to stop the formation of amyloid plaques.[37] Because the amyloid cascade hypothesis is the most widely accepted theory of AD pathogenesis, drugs targeting Aβ are being widely pursued,[38] and tramiprosate was the first to reach late-stage development. The phase 3 trial, which was conducted in 67 centers throughout North America and enrolled 1052 patients with mild to moderate AD, compared tramiprosate 100 bid and 150 mg bid with placebo (continued use of approved AD medications was allowed). The primary end points were the ADAS-cog, the Clinical Dementia Rating-Sum of Boxes (CDR-SB) rating scale, and change in hippocampal volume by MRI.[39] Despite promising results in phase 2 studies, the drug did not demonstrate significant superiority to placebo on any of these outcome measures.[40] In November 2007, the sponsor announced a plan to discontinue the development of tramiprosate as a pharmaceutical, and halted the EU phase 3 trial.[41] One potential explanation for the poor results is that tramiprosate was noted to actually promote the aggregation of tau,[42] which is the primary

component of neurofibrillary tangles, another major pathologic hallmark of AD. Another contributing factor was the unusually large placebo response rate.[40]

Xaliproden (SR57746A)

Two large (N = 1306 and N = 1455), 18-month, clinical trials of xaliproden (monotherapy or adjunctive therapy, respectively) in patients with mild to moderate AD (MMSE, 16–26, inclusive) were completed in 2007.[43] Failure to demonstrate sufficient efficacy in both trials resulted in cancelation of the xaliproden development program for AD in September 2007.[44] Xaliproden is currently being studied as a preventive treatment for chemotherapy-induced neurotoxicity.[45] The drug was thought to be a good candidate for the treatment of AD because of its nerve growth factor–like effects and its antagonism of the serotonin 1A (5-HT_{1A}) receptor.[46] The consideration of 5-HT_{1A} antagonists for AD is based on preclinical data showing that they facilitate both glutamatergic and cholinergic neurotransmission,[47] and that inhibition of the 5-HT_{1A} receptor results in enhancement of cognitive abilities.[48]

ONGOING PHASE 3 TRIALS (Table II)

Despite the disappointing early results in the first wave of phase 3 testing of novel agents for the treatment of AD, there are several other compounds in phase 3 clinical trials at this time, and dozens more in earlier phases of development. The remainder of this article focuses on these potentially groundbreaking new therapies.

Bapineuzumab (AAB-001)

Amyloid plaques are abnormal, insoluble, extracellular aggregates of Aβ peptide and one of the pathologic hallmarks of AD.[49] Immunotherapy, using monoclonal antibodies to Aβ, has resulted in cognitive improvements in mouse models of AD.[50-52] There are several humanized monoclonal antibodies targeting Aβ that are in clinical development. Of these, the only one to have reached phase 3 is bapineuzumab, which is the largest clinical trial program ever undertaken for this indication. A total of 4 independent trials of 18 months' duration, each enrolling approximately 1000 patients with mild to moderate AD, will compare various doses of bapineuzumab with placebo. The primary outcome measures are the ADAS-cog and the Disability Assessment for Dementia (DAD).[53]

Results of a highly anticipated 18-month phase 2 study involving 234 patients who received up to 6 infusions (1 every 13 weeks) of bapineuzumab were reported at ICAD in 2008.[54] The main safety concern to emerge was vasogenic edema, which was noted on MRI, occurred in 12 patients, and resolved in all cases; in 6 cases the patients were reinstated on treatment. Although there were 9 adverse events (AEs) that occurred at a rate of ≥ 5% and more than twice as frequently in the bapineuzumab group compared with placebo, most AEs were mild to moderate and there was no difference in discontinuations due to AEs between the groups. As with most phase 2 studies, this one was not powered to detect efficacy. Nonetheless, there was a trend toward efficacy on the ADAS-cog (2.3-point improvement compared with placebo, $P = 0.078$). When restricting the analysis to patients who completed the trial (n = 78, *APOE ε4* carriers and noncarriers combined), there was a 4.3-point improvement over placebo on the ADAS-cog ($P = 0.003$). Additional post hoc analyses were also performed stratifying for *APOE ε4* status, which suggested that noncarriers fared better than carriers. The phase 3 studies, due for completion in April 2011, should provide definitive answers to the safety and efficacy questions raised by this phase 2 study.

Dimebon

Dimebon, a drug used in Russia for over 2 decades for its antihistaminic effect, is also a cholinesterase and NMDA inhibitor, the 2 mechanisms of action of existing AD drugs.[55]

However, it is now believed that the dimebon's primary mechanism of action in AD is stabilization of mitochondrial function.[56] Dimebon is now in phase 3 clinical trial development, with patient enrollment having begun in the United States, Europe, and South America (final goal, N = 525).[57] This follows the publication of results of a 26-week randomized, double-blind, parallel-group phase 2 study (N = 183) in patients with mild to moderate AD that are highly encouraging.[55] Compared with placebo, treatment with dimebon resulted in significant benefits in ADAS-cog (intent-to-treat–last observation carried forward) at Week 26 (mean drug-placebo difference −4.0 [95% CI, −5.73 to −2.28]; $P < 0.0001$). Moreover, dimebon-treated patients had a significant improvement on ADAS-cog at study end point (mean difference −1.9 [−2.92 to −0.85]; $P = 0.0005$). Data from a 6-month open-label extension study revealed no significant safety or tolerability issues, though depression was reported significantly more frequently in the dimebon group.

LY450139

The neurotoxic Aβ peptide is generated by cleavage of APP by β- and γ-secretases.[58] Inhibitors of γ-secretase thus present an attractive target for AD therapy.[59] Animal studies of γ-secretase inhibitors indicate that such compounds lower the levels of Aβ in the brain.[60,61] LY450139 is the first selective γ-secretase inhibitor in clinical development for treatment of AD to reach phase 3 testing. Enrollment in 2 long-term (at least 18 months' duration) trials comparing LY450139 with placebo has begun and is ongoing, with targets of 1100 patients with mild to moderate AD for one study (uniform titration and dosage of study drug) and 1500 for the other (comparing 100 mg/d or 140 mg/d of study drug with placebo).[62]

A phase 2 study in 51 patients (placebo [n = 15], LY450139 100 mg [n = 22], or LY450139 140 mg [n = 14]) revealed a clinically significant reduction in plasma, but not CSF, Aβ levels in both active treatment groups. Although there were no significant differences in cognitive outcome measures between groups, the trial was not powered to detect such differences and was only 14 weeks in duration. Safety concerns were noted, including 1 case of transient bowel obstruction and 3 possible drug rashes. Because LY450139 inhibits NOTCH protein, there is a need for hematologic monitoring.[63]

Rosiglitazone

Insulin, insulin receptors, and insulin-sensitive glucose transporters are abundant in the medial temporal regions of the brain that support the formation of episodic memory.[64] Insulin signaling, therefore, is now known to play a role in memory functions and may also participate in the regulation of APP and Aβ.[65] In addition, Aβ accumulation in the brains of patients with AD may be due to impaired Aβ-degrading enzymes, including insulin-degrading enzyme.[66] These findings indicate that CNS insulin-related abnormalities may cause or exacerbate cognitive impairments, and that the treatment of insulin resistance may reduce the risk or delay development of AD.[65] The leading drug in clinical development that is based on the insulin resistance hypothesis is rosiglitazone, the peroxisome proliferator–activated receptor-γ agonist originally developed for management of diabetes. In a small pilot study of rosiglitazone in patients with mild AD or aMCI (N = 30), measures of delayed recall and selective attention were significantly better in rosiglitazone- vs placebo-treated patients.[67] Recent concerns regarding the safety of rosiglitazone (and pioglitazone) in patients with or without a history of heart failure have been raised, particularly if they are used in conjunction with insulin. This development does not seem to have impacted the clinical trial program for rosiglitazone in patients with AD, in part because a diagnosis of diabetes mellitus is an exclusionary criterion.

The phase 3 clinical trial for rosiglitazone is large, comprising 1 monotherapy trial (N = 863) with an active comparator (donepezil) and placebo arm that was just completed,[68] and 2 adjunctive therapy trials, each with an enrollment target of 1400 patients, with open-label

extensions following the double-blind phase of each trial.[69] The primary outcome measures in each of these trials are the change from baseline in ADAS-cog total score and CIBIC-plus caregiver input score at Week 24, as a function of *APOE* ε4 status. This prespecified stratification by ApoE status is based on the results of the successfully competed phase 2 trial (N = 511).[70] In that study, there was no significant difference between placebo and rosiglitazone at any of the doses tested (2, 4, or 8 mg/d) for the population as a whole, but there was a significant interaction between ADAS-cog and ApoE status ($P = 0.014$). Among those who were not carriers of ApoE4, exploratory analyses demonstrated significant improvement in ADAS-cog on 8 mg rosiglitazone ($P = 0.024$; not corrected for multiplicity). No serious safety issues were reported in this trial.

COMPLETED PHASE 2 TRIALS (Table III)

Unsuccessful

AN1792—Based on the amyloid cascade hypothesis, active immunization targeting Aβ is a therapeutic strategy that has generated widespread interest. The first-generation Aβ vaccine, AN1792, underwent a large phase 1 trial (N = 80) in which 4 intramuscular injections of 2 doses of AN1792 with adjuvant QS-21 and 2 doses without adjuvant were given during the first 24 weeks, and a polysorbate 80–modified formulation was used for up to 4 additional injections from Week 36 to Week 72.[71] There was 1 case of meningoencephalitis, diagnosed post mortem on study follow-up (Day 219), which was not attributed to study drug. Overall, AEs were reported in 23.9% of those treated with AN1792, with no dose-AE relationship found. Exploratory efficacy analyses identified an efficacy signal on the DAD ($P = 0.002$, all treated patients vs placebo), but not on 3 other outcome measures. However, despite the apparently acceptable safety profile in this study, the subsequent phase 2 study (IM AN1792 225 μg plus the adjuvant QS-21 50 μg, n = 300 and intramuscular saline, n = 72) was discontinued because 6% of participants developed aseptic meningoencephalitis.[72] Immunization was stopped after 1 (2 patients), 2 (274 patients), or 3 (24 patients) injections, at which point only 59 (19.7%) developed the predetermined antibody response. Although no significant differences were found between antibody responder and placebo groups for ADAS-cog, DAD, CDR, MMSE, or Clinical Global Impression of Change (CGIC), a post hoc analysis of the z-score composite across all tests revealed a difference favoring antibody responders (0.03 ± 0.37 vs -0.20 ± 0.45; $P = 0.020$). In a recently published study performed 6 years after completion of the phase 1 study, 8 of 9 patients who received AN1792 and who gave permission for post mortem examinations were assessed neuropathologically.[73] The key finding was that the degree of plaque removal varied significantly with mean antibody response attained during the treatment study period (Kruskal-Wallis $P = 0.02$), and 2 of 8 patients had nearly complete clearance of plaques. However, there was no evidence of improved survival (HR, 0.93; 95% CI, 0.43–3.11; $P = 0.86$) or of a reduction in time to severe dementia (HR, 1.18; 95% CI, 0.45–3.11; $P = 0.73$) in the AN1792 group vs the placebo group. Although the safety problem led to the discontinuation of the AN1792 program, there are many active immunization strategies now being pursued in phase 1 trials.

Lecozotan SR—This compound is a potent, selective 5-HT_{1A} receptor antagonist that had been shown in several primate models to have cognitive-enhancing properties.[48] Two dose-ranging (2, 5, and 10 mg/d), 6-month, phase 2/3 trials (N = 250) of lecozotan SR as add-on treatment to ChEI therapy were completed in June 2008.[74] No data have been published, and the compound is no longer included in a comprehensive list of Wyeth Pharmaceuticals development pipeline.[75]

SGS742—SGS742, a phosphoaminoacid derivative, orally active, selective, $GABA_B$ receptor antagonist,[76] was considered a potential treatment for AD because activation of $GABA_B$

receptors had been shown to inhibit memory/learning in certain animal models. It was hypothesized that $GABA_B$ antagonists might reverse this effect by reducing glutamatergic excitotoxicity via indirect effects on NMDA receptors. In the first phase 2 trial, in 110 patients with MCI,[77] at a dose of 600 mg 3 times daily (tid) for 8 weeks, the drug was well tolerated. In addition, there were significant increases in attention, in particular choice reaction time, visual information processing, and working memory, measured as pattern recognition speed. However, in a larger (N = 280) phase 2b monotherapy trial in patients with mild to moderate AD,[78] the drug failed to meet its efficacy end points.

Successful

Huperzine—Huperzine A, derived from the Chinese herb *Huperzia serrata*, was identified by scientists in China in the 1980s as a potent, reversible, selective acetylcholinesterase inhibitor. More recently, a variety of potential neuroprotective effects have been reported that may also be of benefit for the treatment of AD.[79] In a phase 2 US study completed in November 2007, 210 patients with mild to moderate AD received either 200 μg or 400 μg huperzine A orally bid for 16 weeks.[80] Approximately half the patients were also receiving memantine. Results of the primary end point, the ADAS-cog, showed significant cognitive enhancement at the 400-μg bid dosage, but not at the 200-μg dose. There were no statistical differences between either dose or placebo for the secondary end points Alzheimer's Disease Cooperative Study (ADCS)-CGIC, and the Neuropsychiatric Inventory. However, there was a trend toward a positive response on the ADCS-activities of daily living (ADL) scale with huperzine 400 μg bid ($P = 0.08$). In addition, the drug was safe and well tolerated during the trials, particularly given that many of the patients in this study did not tolerate at least 1 prior treatment trial using a marketed ChEI.[81] A phase 3 trial is anticipated.

Intravenous Immunoglobulin (IVIg)—There is evidence that IVIg could be useful as a treatment for AD as it contains antibodies against Aβ.[82] A 6-month, open-label pilot study of IVIg in 5 patients with mild AD, all of whom were receiving stable doses of ChEIs, and in some cases also memantine, resulted in improved cognition.[83] This finding was confirmed and extended in 8 patients with mild AD in a phase 2, 18-month, open-label trial comprising a 6-month dose-finding phase, a 3-month discontinuation phase, and a 9 month-treatment phase, which demonstrated transient improvements on both cognitive and global clinical measures during the initial phase, a return to baseline in the second phase, and stabilization in the final phase.[84] A phase 3 clinical trial is planned.

Methylthioninium Chloride (MTC, TRx0014)—In contrast to the mostly disappointing results presented at ICAD 2008, the main positive surprise was the unanticipated report of a highly successful phase 2 trial of TRx0014, a proprietary formulation of a very old and well known drug, MTC, or methylene blue.[85] MTC is a deep blue dye used as a tissue stain in biology, as well as in analytical chemistry and in numerous industrial products (eg, ink). Its use as a treatment for AD is based on its reported ability to interfere with tau aggregation by acting on self-aggregating truncated tau fragments. Data presented at ICAD 2008 from unpublished preclinical studies showed that MTC dissolved tangle filaments isolated from brain with an effective concentration (EC50) of 0.15 μmol/L and stopped tau aggregation in cells with an EC50 of 0.56 μmol/L.

In the phase 2 trial, 323 patients with mild to moderate AD who were not receiving any AD pharmacotherapy were randomized to 1 of 3 doses of TRx0014 (30, 60, or 100 mg tid, by mouth) or placebo.[86] The primary efficacy end point was ADAS-cog at 24 weeks. Although stratification by AD severity may not have been prespecified in the statistical analysis plan, the results as presented were divided into mild and moderate AD subgroups. On the primary outcome measure, only the moderate AD group demonstrated a significant benefit (a 1.5-point

decline vs a roughly 5.5-point decline for the placebo group, resulting in an approximately 4-point treatment effect).[87] At 50 weeks, the combined mild and moderate groups receiving 60 mg tid had declined 1 point on ADAS-cog, compared with 3.5 points for the 30 mg tid group and 7 points for the placebo group. Finally, at 81 weeks (preliminary data from the open-label extension study); the 60 mg tid group appeared to have stabilized. A highly anticipated phase 3 trial is to begin in 2009.

ONGOING PHASE 2 TRIALS (Table IV)

ABT-089

ABT-089, a selective α4β2 neuronal nicotinic receptor (NNR) agonist, has been evaluated in 5 phase 1 studies, exhibiting favorable pharmacokinetics and tolerability, and 2 phase 2a studies, demonstrating potential for cognitive benefit in patients with mild to moderate AD.[88] A large, dose-ranging (6 dosage regimens vs placebo) phase 2b trial was initiated in late 2007.[89]

ACC-001

Despite the failure of active immunization with AN1792 to demonstrate safety or efficacy in phase 1 and phase 2 trials, the therapeutic rationale for this approach remains strong. ACC-001 is a second-generation vaccine, designed to have an improved safety profile, now undergoing evaluation in 3 separate phase 2 studies with a combined enrollment target of 316 participants with mild to moderate AD, including a small study in Japanese patients. Three dosage regimens, with and without the adjuvant QS-21, are being compared with adjuvant alone and placebo.[90]

AZD3480—Evidence that NNRs may play a role in AD pathophysiology comes from several sources. Loss of nicotinic receptors has been observed in the cortex and striatum in post mortem brains of AD patients.[91,92] The loss of nicotinic receptors is less in former smokers with AD, and former smokers also show less plaque formation.[93] In vitro studies have shown that nicotine protects against cytotoxicity induced by excitotoxins and Aβ[94] and prevents aggregation of monomeric Aβ peptides into β-pleated sheets.[95] In addition, several short-term clinical studies that assessed the effect of the administration of nicotine to patients with AD found improvements in cognition.[96]

AZD3480, an α4β2 NNR subtype nicotinic agonist,[97] was the first of this class of drugs to be evaluated for the treatment of AD in a phase 2b trial, but the results, reported in September of 2008, were inconclusive. Patients with mild to moderate AD (N = 659) were randomized to receive 1 of 3 dosages of AZD3480, donepezil, or placebo in this 12-week trial. Although AZD3480 exhibited an overall safety and tolerability profile comparable to placebo, and was associated with fewer gastrointestinal-related AEs than donepezil, neither AZD3480 nor donepezil met the trial's criteria for statistical significance on the primary outcome measure (ADAS-cog).[98] Future development of AZD3480 for this indication is uncertain.

CAD106

CAD106 is also an active immunization agent. Two small phase 2 studies (N = 30 each) are in progress.[99] Results of the phase 1 program were presented at ICAD in 2008.[100]

CX717—This agent belongs to a therapeutic class known as ampakines, which are positive allosteric modulators of AMPA-type glutamate receptors.[101] Although ampakines have been demonstrated to reduce age-associated memory deficits in animal models,[102] the clinical development of the first ampakine to be evaluated in humans (CX516) was discontinued in phase 2[103]; however, CX717, a second ampakine, is being tested in a pilot phase 2 study designed to assess 2 different CX717 doses in mild to moderate AD, with each patient receiving

psychometric tests and positron emission tomography scans at different time intervals while on active drug or placebo.[104]

DEBIO-9902

DEBIO-9902, a long acting implantable formulation of huperzine A, is being evaluated in a phase 2 trial that completed enrollment as of October 2008.[105]

ELND005 (formerly AZD 103)

ELND005 is a cyclohexanehexol stereoisomer, scyllo-inositol. Inositol comes in 8 possible stereoisomeric forms, of which 3 are found in human brain, including myo-inositol, the most common form that is also available as a nutraceutical. Only scyllo-inositol has been shown to reduce the accumulation of soluble Aβ oligomers in the brain of transgenic mice and reverse memory deficits.[106] Having successfully completed phase 1 trials, a phase 2 trial (N = 340) is under way to assess the safety and efficacy of 3 dosages of ELND005 vs placebo, with results expected by mid-2010.[107]

Insulin (Intranasal)

Reduced brain insulin signaling and low CSF-to-plasma insulin ratios have been observed in patients with AD.[64] After intranasal administration, insulin-like peptides follow extracellular pathways to the brain within 15 minutes.[108] A randomized, double-blind, placebo-controlled, 3-week pilot trial in was performed in 25 patients with early AD or aMCI, given intranasal insulin 20 IU bid (n = 13) or placebo (n = 12). Cognitive and laboratory testing was performed at baseline and after 21 days of treatment. The insulin group demonstrated significantly superior scores on measures of working memory ($P = 0.0374$), attention ($P = 0.0108$), and functional status ($P = 0.0410$). Insulin treatment also significantly increased the Aβ 40/42 ratio ($P = 0.0207$).[108]

Given these encouraging findings, there are now 2 phase 2 trials of intranasal insulin in progress: a university-based trial of Insulin Aspart (N = 36),[109] and a larger trial (N = 90), conducted at the National Institutes on Aging, appropriately designated SNIFF 120 (Study of Nasal Insulin to Fight Forgetfulness [120 days]).[110]

Lithium

Glycogen synthase kinase-3 (GSK-3) activity has been associated with AD because of its role in the phosphorylation of tau and the regulation of the production of Aβ[111,112] Lithium has been shown to inhibit GSK-3 activity[113] and to provide a significant and dose-dependent reduction in the expression of GSK-3, which was specific to hippocampal cells.[114] Despite this interesting basic science knowledge, no further clinical development has been pursued following the completion in 2005 of a small phase 2 trial (N = 35).[115] Ongoing concerns about the safety, tolerability, and monitoring requirements associated with the clinical use of lithium are a serious impediment to further development of lithium for prevention of AD.[114] Nonetheless, a recent case-control study found a significantly reduced incidence of AD in patients with bipolar disorder receiving lithium compared with a matched population not receiving lithium (5% vs 33%; $P < 0.001$, background incidence 7%), suggesting that there is an increased incidence of AD in patients with bipolar disorder and that lithium reduces the incidence of AD to that observed in the general population.[116]

LY2062430 (Solanezumab)

LY2062430 is another monoclonal antibody against Aβ peptide that has entered phase 2 trials, one of which was completed in May of 2008. These studies should help determine optimal dosing of this agent.[117]

MEM 3454

This compound is a partial nicotinic α7 receptor agonist, which successfully completed a phase 2a trial in 80 patients with mild to moderate AD. Three dosages of MEM3454 were evaluated; the 2 lower dosages (5 and 15 mg/d) provided significant improvement ($P < 0.05$) on several efficacy measures. Moreover, constipation was the only AE significantly more common in the treatment groups (43%) compared with placebo (5%), and there were no serious AEs attributed to the drug.[118] Further development of this agent is expected.

MK-0952

Phosphodiesterases (PDE) are an important family of proteins that regulate the intracellular level of cyclic adenosine monophosphate. PDE4 inhibitors are neuroprotective, neuroregenerative, and anti-inflammatory agents, and preclinical studies have indicated that PDE4 inhibitors can counteract deficits in long-term memory caused by overexpression of mutant forms of human APP.[119] A phase 2 trial of the PDE4 inhibitor MK-0952 for mild to moderate AD was completed in late 2007[120]; results have not yet been published.

PBT2

PBT2 is a metal-protein attenuating compound that affects the $Cu^2(+)$-mediated and $Zn^2(+)$-mediated toxic oligomerization of Aβ seen in AD. As such it is considered an antifibrillar agent with a unique mechanism of action. A 12-week phase 2a trial (N = 78) in patients with early AD completed in December 2007 demonstrated that PBT2 dose dependently ($P = 0.023$) reduced CNS $A\beta_{42}$ levels (difference in least squares mean change from baseline between PBT2- vs placebo-treated patients was −56.0 pg/mL, 95% CI, −101.5 to −11.0; $P = 0.006$). [121] No serious AEs were reported by patients taking PBT2, and 95% of patients completed the study. Cognitive testing, which included ADAS-cog, MMSE, and a neuropsychological test battery, showed significant improvement over placebo in the PBT2 250 mg group only for 2 components of the neuropsychological test battery, but the trial was not powered for efficacy end points and was only 12 weeks in duration.

PF-04360365

This agent, like bapineuzumab, is a monoclonal antibody against Aβ. Although phase 1 studies are not scheduled to be completed until 2009, recruitment for a small phase 2 trial (N = 100) began in October 2008.[122]

PF04494700 (Formerly TTP488)—The receptor for advanced glycation end products (RAGE), besides possessing perhaps the best acronym of any CNS receptor, has been shown to bind to Aβ and mediate its transport across the blood brain barrier.[123] More recently, a series of elegant experiments in mouse brain slices of entorhinal cortex (the first area of the brain to exhibit damage in AD) has shown that the RAGE-Aβ complex suppresses long-term potentiation, at least in part via activation of p38MAP.[124] The clear implication of this evolving scientific understanding is that an inhibitor of RAGE could provide therapeutic benefit in AD. Accordingly, a large (N = 400) phase 2 safety and efficacy trial is now under way, examining 2 dosage schedules of PF04494700 in patients with mild to moderate AD.[125]

PRX-03140

PRX-03140 is a novel, highly selective, small-molecule agonist of 5-HT4, a specific G-protein coupled receptor.[126] In phase 2a clinical trials of PRX-03140 as a single agent and in combination with donepezil in patients with mild AD, patients receiving daily oral 150 mg doses of PRX-03140 as monotherapy achieved a mean 3.6-point improvement on the ADAS-cog vs a 0.9-point worsening in patients taking placebo ($P = 0.021$). PRX-03140 was well tolerated as monotherapy and in combination with donepezil, with no serious drug-related AEs.

In preclinical studies, PRX-03140 has been shown to improve cognitive function through increasing levels of acetylcholine, soluble APP, and brain-derived neurotrophic factor in regions of the brain known to be important for memory. A phase 2b program started in April 2008 (6-month combination therapy trial)[127] and May 2008 (3-month monotherapy trial).[128]

Raloxifene

Raloxifene, a selective estrogen receptor modulator, is approved at lower doses for treatment and prevention of osteoporosis in postmenopausal women. In a trial of 120 mg/d raloxifene in 5386 postmenopausal women at risk for osteoporosis, a cognitive outcome study demonstrated a reduction in risk for either MCI (relative risk = 0.67) or AD (relative risk = 0.52).[129] This finding, supported by a body of evidence suggesting that estrogen may have a protective effect against dementia,[130] led to the clinical development of raloxifene for treatment of AD. The current phase 2 trial (N = 72) is a 1-year comparison of raloxifene 120 mg/d vs placebo in patients with early AD.[131]

SB742457

Another compound that targets a serotonin receptor, a small molecule antagonist of 5HT6, is now in a second round of phase 2 testing.[132] Antagonists of 5HT6 have been shown in preclinical studies to variably enhance cholinergic, glutamatergic, noradrenergic, and dopaminergic neurotransmission and, in human studies, to provide benefit in several learning and memory tests.[133] Following the successful completion of 2 dose-ranging, safety studies in patients with mild to moderate AD,[134] 2 larger phase 2 trials, 1 as add-on therapy to donepezil and 1 as monotherapy, were started in 2008 (N = 672 and N = 576, respectively).[135]

SK-PC-B70M

This compound is composed of the oleanolic-glycoside saponins enriched fraction from *Puksatilla koreana* (Korean Pasque Flower). It has been shown to have neuroprotective and cognition-enhancing effects in animal models.[136] A phase 2 study (N = 188) comparing SK-PC-B70M monotherapy with placebo is nearing completion in early 2009.[137]

T-817MA

In vitro studies with T-817MA have demonstrated its potent neuroprotective effect against Aβ or oxidative stress–induced neurotoxicity, as well as its promotion of neurite outgrowth in rat hippocampal slice cultures.[138] These neuroprotective and neurotrophic properties suggest that it may be useful in the treatment of AD. A large (N = 316) phase 2 study, initiated in April 2008, is powered to detect an efficacy signal using the ADAS-cog as a primary outcome measure, in addition to assessing its safety and tolerability in patients with mild to moderate AD.[139]

ONGOING PHASE 1 TRIALS

The agents identified in this section (Table IV) comprise a broad representation of compounds in phase 1 trials as of January 2009, including agents with presumptive mechanisms of action similar to those of compounds in more advanced stages of development, as well as a number of agents with novel mechanisms of action. However, because phase 1 trials are designed almost exclusively to assess safety in human populations and because there is a long time span between phase 1 testing and the potential introduction of a new therapy into clinical practice, more detailed information on agents in this phase of clinical development is not particularly relevant to clinicians.

CONCLUSIONS

The clinical development of novel agents for the symptomatic and disease-modifying treatment of AD has shown both promise and disappointment. Despite the lack of introduction of a novel compound for the treatment of AD since memantine in 2002, the breadth and depth of the clinical development pipeline—at all phases of development—is considerable. The sheer variety of drug targets and mechanisms of action of these novel agents, as well as the total number of compounds under investigation, makes it highly likely that over the course of the ensuing decade important new pharmacotherapeutic options will become available for the treatment of AD. Moreover, research into the underlying etiology and pathophysiology of AD is likely to facilitate the identification of additional targets for future drug development.

In the meantime, it is important not to underestimate the value of currently available treatments, and to ensure that every patient with AD is prescribed optimal pharmacotherapy as early in the course of the disease as possible. Furthermore, many agents in clinical development for the treatment of AD today are being evaluated in patient samples in which the majority is receiving at least 1 ChEI. Because concurrent therapy is not an exclusionary criterion in most trials, patients can often enroll in trials while receiving a ChEI and memantine. Indeed, making patients and their caregivers aware of clinical trials that are taking place in their geographical area is an important component of providing optimal clinical care, and may help to accelerate advances in treatment.

It is too soon to predict which therapeutic strategy, or which particular agent, will be the next to expand our treatment options for patients with AD. However, it is certainly not premature to claim that from this crowded and fascinating pipeline of novel compounds there will emerge several medications that will help revolutionize the treatment of AD and transform it from a relentless progressive and devastating illness to a manageable chronic disease.

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Table I

Completed phase 3 clinical trials.

Agent	No. of Patients in Trial(s)	Mechanism of Action	Monotherapy or Add-on to ChEI and/or Memantine
Atorvastatin[29]	600	HMG CoA reductase inhibitor	Add-on
Ginkgo biloba[3]	3069*	unknown	Monotherapy
NSAIDs[14-18] (rofecoxib, celecoxib, naproxen)	>2500	Antiinflammatory	Both
Phenserine[21]	364	ChEI, inhibits Aβ formation	Monotherapy
Simvastatin[32]	400	HMG CoA reductase inhibitor	Add-on
Tarenflurbil[35,36]	1600	SALA	Both
Tramiprosate[40,41]	1052	Antifibrillar	Both
Xaliproden[43-45]	2761	Serotonin antagonist, nerve growth factor effects	Both

*Patients had aMCI or normal cognition.

Methodology of all trials listed is standard randomized, placebo-controlled, double-blind, parallel-group unless otherwise stated.

Table II

Ongoing phase 3 trials.

Agent	Date of Actual/Expected Trial Completion	Mechanism of Action
Bapineuzumab (AAB-001)[53,54]	2010–2011	Passive Aβ immunization
Dimebon[55,57]	2010	Stabilizes mitochondrial function
LY450139[62,63]	2012	Gamma secretase inhibition
Rosiglitazone[68,69]	2009–2010	Peroxisome proliferator–activated receptor

Table III

Completed phase 2 trials.

Agent	Date of Trial Completion	Mechanism of Action
FAILED		
AN1792[71,72]	2003	Active Aβ immunization
SGA-742[78]	2005	$GABA_B$ receptor antagonist
Lecozotan SR[74]	2008	Selective 5-HT_{1A} receptor antagonist
SUCCESSFUL		
Huperzine A[79,80]	2007	ChEI
Intravenous immunoglobulin (IVIg)[84]	2008	Passive immunization
Methylthioninium chloride (TRx0014)[86,87]	2008	Dissolves and inhibits formation of neurofibrillary tangles

Table IV

Ongoing phase 2 trials

Agent	Date of Actual/Expected Trial Completion	Mechanism of Action
ACC-001[90]	2012	Active Aβ immunization
CAD106[99]	2010	Active Aβ immunization
PF-04360365[122]	2011	Passive Aβ immunization
LY2062430[117] (solanezumab)	2008*	Passive Aβ immunization
AZD3480[98]	2008*	α4β2-Selective NNR agonist
ABT-089[88,89]	2009	α4β2-Selective NNR agonist
MEM3454[118]	2008*	α7-Selective NNR agonist
SB742457[135]	2009–2010	5-HT6 antagonist
PRX-03140[127,128]	2010	5-HT4 agonist
T-817MA[139]	2010	Neuroprotective and neurotrophic properties
SK-PC-B70M[137]	2008–2009	Neuroprotective and neurotrophic properties
PBT2[121]	2008*	Metal-protein attenuating compound
Insulin[109,110] (intranasal)	2009	Enhances insulin signaling
PF04494700[125]	2011	Receptor for advanced glycation end products inhibitor
Lithium[115]	2005*	Glycogen synthetase kinase 3 inhibition
CX717[104]	NA	AMPA-type glutamate receptor modulator
DEBIO-9902[105]	2009–2010	ChEI (long-acting injection)
ELND005[106]	2010	Inhibition of Aβ oligomer formation
Raloxifene†[131]	2009	Estrogen receptor modulator
MK-0952[120]	2007	Phosphodiesterase-4 inhibitor

*Additional phase 2 study(s) planned or anticipated.

†Women only.

Table V

Agents currently in phase1 trials*

Agent	No. of Patients (No. of Trials)	Mechanism of Action
AFFITOPE AD01 AFFITOPE AD02	48 (2) 48 (2)	Active Aβ immunization
GSK933776A	122 (1)	Active Aβ immunization
MABT5102A	50 (1)	Active Aβ immunization
V950	70 (1)	Active Aβ immunization
R1450	60 (1)	Passive Aβ immunization
RN1219	NA	Passive Aβ immunization
AZD0328	190 (3)	α7-Selective NNR agonist
EVP-6124	48 (1)	α7-Selective NNR agonist
CTS21166	56 (1)	β-Secretase inhibitor
Posiphen	NA	β-Secretase inhibitor and reduces APP production
PAZ-417	156 (4)	Inhibits plasminogen activator inhibitor-1 (increases clearance of Aβ)
GSI-953	153 (3)	γ-Secretase inhibitor
GSK239512	41 (2)	H_3 receptor antagonist
CERE-110	10 (1)	Gene therapy
EVT101	NA	$NR2_B$ subunit containing NMDA antagonist
Nicotinamide (vitamin B3)	50 (1)	Inhibits tau hyperphosphorylation

* Data source for this table is www.clinicaltrials.gov. Accessed Jan 13, 2009