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Current Treatment and Recent Clinical Research in Alzheimer's Disease

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Abstract

The transition from either epidemiological observation or the bench to rigorously tested clinical trials in patients with Alzheimer's disease is crucial in understanding which treatments are beneficial to patients. The amyloid hypothesis has undergone scrutiny recently, as many trials aimed at reducing amyloid and plaque have been completed or are in the testing phase. Examples include modulation of the secretases involved in beta amyloid formation, anti-aggregation agents, and immunotherapeutic trials. Other therapies targeting hyperphosphorylated tau and novel targets such as enhancement of mitochondrial function, serotonin receptors, receptor for advanced glycation end products, and nerve growth factor, as well as other strategies, are discussed. A brief review of the current Food and Drug Administration–approved treatments is included.

Keywords

Alzheimer's disease; amyloid; antioxidant; Dimebon; immunotherapy; receptor for advanced glycation end products; research; secretase; tau; treatment

Altering the course of Alzheimer's disease (AD) could lead to significant pubic health benefits. For example, an intervention that could delay the onset of AD by 2 years would decrease the incidence in such a way that in 50 years there would be nearly 2 million fewer cases than are currently projected.1 One can imagine that significantly altering the course of the disease would similarly sharply decrease the need for nursing home placement and could help patients remain functional for much longer. The costs associated with taking care of a patient with AD increase with disease severity,2 so that if patients could be maintained at an earlier stage, it would be beneficial for the patient, the family, and society. In general, the number of patients with AD is thought to be increasing from approximately 5.3 million in 2009 to 11 to 16 million by 2050.3

There are only 5 medications approved by the Food and Drug Administration to treat AD. Four of them are acetyl cholinesterase inhibitors (donepezil, galantamine, rivastigmine, and tacrine), and the fifth is the *N* -methyl-d-aspartate antagonist memantine. These medications ameliorate the symptoms and can improve the functioning of patients with AD, but they are not curative, nor do they significantly change the course of the illness. The most widely studied treatments aim to address the neuropathological findings over the last century and

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focus on acetylcholine, inflammatory markers, amyloid plaques, and tau-based neurofibrillary tangles. In this article, we discuss some of the drugs that target these and other novel mechanisms and the rationale for some of the most promising new agents, and we review recent findings, both positive and negative, in the treatment and prevention of AD.

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CURRENT FOOD AND DRUG ADMINISTRATION–APPROVED MEDICATIONS

Cholinesterase Inhibitors

Since before 1915, scopolamine, an anticholinergic agent, was used to induce amnesia in women during labor and delivery.[4,5] In the 1970s, research explored the specific cognitive effects of acetylchoine,[6] and trials of physostigmine were undertaken in cognitively normal individuals (eg, Davis *et al*.[7]). Later research was done with AD patients using intravenous and oral physostigmine (eg, Davis and Mohs[8] and Mohs *et al*.[9]). In 1983, the first acetyl cholinesterase inhibitor was approved [tacrine (Cognex)]. It was hampered by 4 times per day dosing, reversible hepatocellular injury in up to 50% of patients, and very poor tolerability due to significant procholinergic side effects of nausea, vomiting, and diarrhea. The other acetyl cholinesterase inhibitors, released between 1996 and 2001, have very similar efficacy, although they have slightly different mechanisms of action. For example, rivastigmine also inhibits butylcholinesterase, and galantamine is an allosteric modulator of the nicotinic receptor. These medications tend to effect a 6- to 18-month improvement in cognitive functioning followed by deterioration along a parallel path. Abrupt cessation of these medications tends to place patients back on their original curve.

Memantine

Memantine is an *N*-methyl-d-aspartate antagonist. It has been approved only for moderate to severe AD, and the Food and Drug Administration refused to extend its approval to mild AD in 2005. In theory, it may help prevent neuronal excitotoxicity. The clinical trials of moderate to severe AD showed a modest improvement in global measures of functioning, both with[10] and without[11] a cholinesterase inhibitor.

Anti-Inflammatory Agents

Overactivity of the immune system, causing damage to neuronal cells, has been postulated to be a mechanism of AD pathogenesis. Neuropathological studies have demonstrated that the brains of AD patients have increased concentrations of acute phase reactants, cytokines, and complement protein in comparison with age-matched controls.[12–15] Epidemiological studies exploring the risk of AD have suggested that nonsteroidal anti-inflammatory or corticosteroid use lessens the risk of developing AD.[16,17] A number of clinical trials have shown no benefit from a variety of anti-inflammatory agents ranging from selective nonsteroidal anti-inflammatory drugs to prednisone as treatments for AD,[18–21] and one recent study has suggested a possible deleterious cognitive effect.[22] Primary and secondary prevention trials with nonsteroidal anti-inflammatory drugs have been similarly negative.[23–25] In addition, there are many side effects of nonsteroidal anti-inflammatory drug use, such as renal insufficiency and gastrointestinal bleeding, which should be noted.

Antioxidants

Oxidative stress has been implicated in cell damage and aging in general26 and in neurodegenerative diseases in particular.27 Thus, medications with antioxidant properties have been evaluated as treatments for AD. Many agents have been examined for their potential benefit in dementia and cognitive improvement on the basis of their antioxidant properties. The most common of these is vitamin E. In one study, vitamin E was found to delay clinical progression in AD patients from moderate impairment to severe impairment, although no cognitive benefit was found.28 Observational studies have reported that the use of high doses of vitamin E may slow progression of AD, and other clinical trials have been unable to demonstrate a benefit in mild cognitive impairment (MCI) or in primary prevention populations.29,30 There remains considerable interest in vitamin E, and 2 important ongoing studies will be informative. One, sponsored by the Department of Veteran Affairs, is a 3-arm study examining vitamin E (100 IU twice daily), memantine, or placebo in a double-blind fashion in a 4-year study of over 800 subjects with mild AD. The primary outcome is a measure of activities of daily living. Another study, Prevention of Alzheimer's Disease by Vitamin E and Selenium (PREADVISE; Clinical-Trials.gov: NCT00040378), is an add-on to a trial to prevent prostate cancer with 35,533 participants, the Selenium and Vitamin E Cancer Prevention Trial (SELECT), which was halted in 2008 because in an interim analysis there were no significant differences between the groups in prostate cancer prevention, although there was an insignificantly increased risk of prostate cancer in the vitamin E group and an insignificantly increased risk of type 2 diabetes in the selenium-only group.31 The PREADVISE study continues to follow over 5000 individuals who had been taking vitamin E (400 IU) alone or in combination with 200 μg of selenium or placebo and will determine how exposure to these affected the risk of developing dementia. Although some safety concerns have been raised about the use of high-dose vitamin E in populations at risk for cardiovascular disease, there is no evidence of negative effects on cognition.

Cholesterol Lowering

Initially, epidemiological studies suggested a decreased risk of AD in patients taking 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors (statins).32,33 Basic research supported the idea that statins may inhibit beta amyloid (Aβ) formation in vitro.34 The initial findings led to clinical research. In a single-site, double-blinded, placebo-controlled, randomized clinical trial of 67 subjects with mild to moderate AD, atorvastatin was shown to have a beneficial effect on cognitive measures in comparison with placebo.35 When the researchers performed secondary analyses, they found that the benefit was more prominent for individuals with baseline elevated cholesterol levels and milder memory impairments.36 Simvastatin, which has reasonable central nervous system penetration, was also associated with a decrease in cerebrospinal fluid α- and β-cleaved soluble amyloid precursor protein (sAPP) but not Aβ (42) after 12 weeks of 20 mg daily.37 When these preliminary data were subjected to a larger multicenter trial lasting for 18 months with 406 patients with AD, statins failed to show a benefit over placebo for simvastain.38 A more recent meta-analysis of epidemiological studies failed to support the beneficial effect of statins on AD risk.39 Large multicenter trials of statins for the prevention of cardiovascular disease, looking at cognitive outcomes, have also shown a lack of a beneficial effect on cognition or incident dementia.40,41

Estrogen

Beginning in the 1930s, studies have examined the possible role of estrogen in cognition.42 In the 1990s, there was a great deal of interest in a number of population and case control studies looking at estrogen usage and the risk of AD. Many of these studies (eg, Paganini-Hill and Henderson,43 Tang *et al*.,44 and Kawas *et al*.45) suggested a decreased risk of AD

with estrogen use, although others (eg, Barrett-Connor and Kritz-Silverstein,46 Barrett-Connor and Edelstein,47 and Brenner *et al*.48) did not. Basic science supported the idea that estrogen might be neuroprotective. Estrogen enhances neuronal growth and connectivity and has been shown to promote neuronal survival (eg, DeVoogd and Nottebohm49 and Matsumoto and Arai50), and it up-regulates nerve growth factor (NGF) messenger RNA and neuronal sensitivity to NGF.51 Early small open-label treatment studies suggested a positive effect of estrogen on cognition in AD. However, results from randomized clinical trials of conjugated equine estrogen (CEE) in women already diagnosed with mild to moderate AD52⁻54 have failed to demonstrate improvement of cognition or a slowed rate of cognitive decline. The duration of follow-up in these studies ranged from 4 to 12 months. There was some evidence of deleterious cognitive effects. The use of CEE to treat AD in postmenopausal women is therefore not recommended. The question of whether estrogen would prevent cognitive loss and AD has also been addressed in prospective trials. Surprisingly, the use of estrogen was associated with both increased cardiovascular risks and increased risk of dementia. For example, in women over 65 years, the use of estrogen or estrogen/progesterone actually increased the odds of converting to MCI or dementia.55,56 A recent randomized trial of CEE in 180 women, less than 1 year after menopause, who were 45 to 55 years old was designed to answer the question of whether the timing of estrogen exposure (ie, perimenopausal exposure) was important in reducing dementia risk. However, this study demonstrated a trend toward worsening cognition in the treated group.57 These results make it difficult to imagine any cognitive benefit from exogenous estrogen. Despite these results, the question of whether estrogen in another form may be useful is being considered in studies of raloxifene, a selective estrogen receptor modulator: in a secondary outcome analysis of an osteoporosis trial of 5386 postmenopausal women taking raloxifene or placebo, it was suggested that at 120 mg there was a lower relative risk of any cognitive impairment (relative risk = 0.73, 95% confidence interval = 0.53–1.01).58 There is a current phase 2 trial (NCT00368459) underway in patients with AD, and it aims to enroll 72 patients at 2 sites.59 Raloxifene has been associated with an increased risk of venous thromboembolism.

Docosahexanoic Acid

Docosahexanoic acid (DHA) is an omega 3 polyun-saturated fatty acid found in fish and some marine algae. It is a component of synaptic plasma membranes and in animal studies has been shown to perform a number of roles in the brain, including affecting the rate of signal transduction, being neuroprotective, and regulating gene expression. Research has suggested that AD patients have lower plasma DHA levels. A clinical trial in Sweden that was published in 2006 found that in patients with very mild AD, omega 3 fatty acids slowed cognitive decline, as evaluated by the Mini-Mental State Examination (MMSE), over a 12-month period, although no effect was seen in patients with moderate stage disease.60 There have been 2 recent trials, one in AD and one in elderly adults with a memory complaint. The AD trial was an 18-month phase 3 trial looking at DHA and the progression of AD in 402 patients who had low dietary intake of DHA (ClinicalTrials.gov: NCT00440050). The 2 outcome measures, a cognitive outcome [Alzheimer Disease Assessment Scale–Cognitive (ADAS-Cog)] and a global one (Clinical Dementia Scale–Sum of the Boxes), as well as other behavioral outcome measures did not differ between the placebo and active groups, despite increased levels of DHA in the serum and cerebrospinal fluid. There was no difference between the mild and moderate AD patients, but those without the apolipoprotein E4 allele did have a statistically slower rate of decline with DHA.61 The other trial was a 6-month trial of DHA versus placebo in 485 elderly patients with a memory complaint. The primary outcome measure was a visuospatial episodic memory test. The active group made significantly fewer errors in comparison with their baseline scores.61 Another trial looking

at high-dose and low-dose DHA and eicosapentaenoic acid in cognitively healthy older adults showed no cognitive benefit over the 26 weeks of the trial.62

Ginkgo Biloba

Ginkgo biloba, a Chinese herbal medicine used for its "healthful properties," including effects on memory, was evaluated to see if it decreased the incidence of all-cause dementia in elderly patients.63 Three thousand individuals, approximately 16% of whom met criteria for MCI at the start of the trial, were followed for a median of 6 years on placebo or ginkgo. Over the duration of the trial, they were evaluated for incident dementia every 6 months. The rates of dementia in general, of AD in particular, and of conversion to dementia from MCI were not statistically different in the 2 groups. They did not report data on specific cognitive measures for individuals in the 2 groups. There was no improvement on any secondary outcomes such as overall morbidity. As pointed out in an editorial concerning this trial, potentially serious side effects of gingko, such as increased bleeding risk, need to be considered in light of the fact that there is no convincing evidence that it has any beneficial effects on cognition or dementia incidence in humans in the forms in which it has been used. 64 A 1-year randomized, placebo-controlled trial of 309 AD patients looking at ginkgo biloba as a treatment for AD showed modest improvement on some measures,65 although 2 later 6-month trials of 21466 and 51367 patients showed no benefit. Overall, the research on ginkgo is at best "inconsistent and unconvincing."68

Homocysteine/B Vitamins

The Framingham study and others have noted that elevations in plasma homocysteine are a risk factor for cardiovascular disease69,70 and cerebrovascular disease71 as well as AD.72 For example, a study of 1092 subjects observed that elevated homocysteine was an independent risk factor for AD, and levels over 14 μmol/L almost doubled an individual's risk of developing AD.72 Theories about how homocysteine might act as a risk factor for AD range from potentiating Aβ production or toxicity to vascular-related effects. To see if lowering homocysteine in patients with AD would change the course of the illness, an 18-month prospective trial in 400 mild to moderate AD patients evaluated the effect of lowering homocysteine. The intervention (folate and vitamins B6 and B12) was quite successful at lowering homocysteine, but it did not slow cognitive decline, and there was no difference between the active and placebo groups in the rate of change of a cognitive measure (ADAS-Cog).73 This was confirmed in another study that also looked at plasma Aβ levels in 300 patients with strokes; again, despite lowering homocysteine, it did not affect the Aβ levels or cognition.74

Xaliproden (SR57746A)

Xaliproden is a compound with has neurotrophic effects in virto. It also antagonizes the 5HT1A receptor75 which may facilitate glutamatergic and cholinergic neurotransmission.76 Unfortunately, the results of 2 large 18-month clinical trials of xaliproden (over 1000 patients in each trial) as both monotherapy and adjunctive therapy for mild to moderate AD yielded disappointing results, and the company is not developing the drug further for these indications.77

AGENTS CURRENTLY UNDER INVESTIGATION

In this section, we discuss avenues currently under investigation, and we group them either by the mechanism if the mechanism is clear or by the agent itself.

Interventions Targeting Amyloid

Amyloid: A Short Review—The only known genetic forms of AD are caused by mutations in amyloid precursor protein (APP) or the enzymes that are involved in Aβ formation. APP is coded on chromosome 21. Individuals with Down syndrome (trisomy 21) are noted to universally have the neuropathological hallmarks of AD as they age. APP is cleaved either by α-secretase into a soluble fragment (sAPP) or by β secretase [also called β-site amyloid precursor protein–cleaving enzyme (BACE)] and then by γ-secretase, and this results in fragments that are 37 to 42 amino acids in length. The 42–amino acid fragment is most associated with AD pathology. The only known autosomal dominant forms of AD are due to mutations in either APP or regions that code for proteins involved in the secretases, and they are all associated with elevations in Aβ. Because of this genetic evidence, many scientists postulate that the accumulation of Aβ is the inciting factor in the development of AD. The Aβ fragments can either oligomerize to form soluble toxins or else fibrillize to form plaques. Aβ oligomers may play an important role in AD pathogenesis, as they have been found to be highly toxic to neurons by initiating a cascade of events that contribute to activation of microglia, synaptic degeneration, oxidative injury, and apoptosis. Interventions aimed at reducing amyloid plaque burden by either altering amyloid metabolism through enzyme mediation or maximizing clearance, particularly through immunotherapy, are under study (reviewed by Barten and Albright78).

> The only known genetic forms of AD are caused by mutations in amyloid precursor protein (APP) or the enzymes that are involved in amyloid beta (Aβ) formation.

Modulating the Formation of Aβ—If the overproduction or accumulation of Aβ is in fact the crucial event in the cascade that leads to AD, then decreasing its production by the inhibition of BACE or γ-secretase or the enhancement of α-secretase should decrease the pathology and change the course of the illness. Research has been done to identify and modulate the secretases. The greatest concern about inhibiting secretases, which have been highlighted in animal models and early trials, is the other potentially important proteins that they may be involved in processing. Thus, toxicities must be carefully monitored with these agents.

There are a number of BACE inhibitors that have been described in animal models but have not yet arrived in human trials. A number of approaches, including the creation of novel antibodies to target the BACE cleavage site of APP, have been taken.

The research into the γ-secretases has progressed farther, with 1 medication in phase 3 clinical trials. One concern about the γ-secretases is that they are involved in the cleavage of the Notch transmembrane receptors. In animal models, chronic inhibition is associated with effects in the gastrointestinal system, thymus, and spleen.

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The agent in phase 3 trials is LY450139 from Eli Lilly. The phase 2 study79 of 70 AD patients, lasting 6 weeks, demonstrated relative tolerability and decreased plasma levels of Aβ. Two phase 3 trials that are currently recruiting are looking at different doses in comparison with placebo (ClinicalTrials.gov: NCT00762411 and NCT0059456). Other γ-secretase inhibitors in clinical trials include one from Bristol-Myers Squib (BMS-708 163),

which is relatively Notchsparing according to preclinical testing. There are 2 ongoing clinical trials with this agent (Clinical-Trials.gov: NCT00810147 for patients with mild to moderate AD and NCT00890890 for those with prodromal AD). In addition, Wyeth is testing GSI136 in a phase 1 trial (ClinicalTrials.gov: NCT00718731).

Other agents serendipitously have been found to be secretase inhibitors. For example, tarenflurbil, an anti-inflammatory agent, was found to modulate γ-secretase activity. Basic research suggested cognitive benefit in animal studies. The year-long phase 2 trial of 210 patients with mild to moderate AD demonstrated tolerability, but it did not show a beneficial effect on function or cognition. In a post hoc analysis, some benefit was seen at the highest dose in the patients with the mildest disease80 An 18-month phase 3 trial with 1649 patients showed no benefit from treatment, and the company (Myriad) discontinued the investigation of the agent.81 It has been postulated that the oral administration of the medication may not have allowed for adequate γ-secretase inhibition to affect disease.82

Blocking the Aggregation of Beta Amyloid into Oligomers or Amyloid Plaque—The amyloid hypothesis posits that aggregated Aβ is particularly toxic to cells, and thus blocking aggregation and ultimately preventing plaque from forming could change the course of the illness. The most interesting agent in trials is scyllo-inositol, which is currently in phase 2 clinical studies sponsored by Elan Pharmaceuticals (ClinicalTrials.gov: NCT00568776). This agent seems to be directed at the Aβ oligomers: it binds them and prevents synaptic damage. Scyllo-inositol is a small molecule that readily crosses the blood-brain barrier by active transport. A recent negative trial of anti-aggregation agents was 3APS [tramiprosate or homotaurine (Alzhemed from Neurochem)]. The phase 3 trial in the United States was inconclusive; it failed to demonstrate efficacy on the cognitive endpoints in the 18-month trial of 1052 patients. The company then halted the European phase 3 trial before the data were released, and the results of the 2 trials have not been published except in a non–peer-reviewed article on the columetric magnetic resonance imaging results, which suggested less hippocampal shrinkage.83 Citing the magnetic resonance imaging findings, the company has decided to promote this medication as an over-the-counter medication, Vivimind, which is being put forward as protecting against memory loss.84

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Increasing Clearance of Beta Amyloid with Immunotherapy—Specific antibodies can bind Aβ and promote its clearance from the central nervous system. This can be accomplished either by the introduction of Aβ as an antigen so that the body can produce antibodies to it (active immunotherapy) or by the use of preformed antibodies (passive immunotherapy.) In 2002, the first phase 2 active immunity trial (AN-1792) was halted because of meningoencephalitis in 6% of the patients who received the vaccine (Clinical-Trials.gov: NCT00021723). This trial of 372 patients used an aggregated amyloid peptide with an adjuvant (QS-21) to boost the immune response. Researchers postulated that T cell–mediated immunity caused this adverse reaction, and thus the second-generation agents currently in trials use an N-terminal fragment of Aβ as an antigen because it is thought that this will generate more B cell–mediated, humoral immunity. The T cell–stimulating epitopes

are more distal. Despite the halting of the trial, the researchers did follow the patients who received the vaccine. It is interesting to note that less than 20% of those who received the active vaccine achieved the targeted immune response level.85 In those that did, there was a marked effect on amyloid in the brain, although the other neuropathological hallmarks of AD were unchanged in comparison with controls, with prominent tangles, neuropil threads, and cerebral amyloid angiopathy.86 Unfortunately, there was little evidence of significant cognitive benefit as measured by both the ADAS-Cog and MMSE. However, with a composite statistical measure on the Neuropsychological Test Battery, there was some suggestion of benefit. With respect to functional measures, the patients who mounted the antibody response and the placebo controls declined at similar rates. There was some suggestion of improvement on a quality-of-life measure in the active group.85

Given the significant changes in plaque burden seen on autopsy, there was speculation about why there was little cognitive and functional change seen in the patients who mounted an antibody response. First, it is possible that removing Aβ after AD has already progressed is not useful; rather, it must not be allowed to accumulate in the first place. A second possibility is that Aβ is not the central player that it is thought to be, and other targets might be more fruitful. Third, the small number of patients who responded to the vaccine may limit the trial's generalizability. Had the patients responded to the vaccine safely and had the full set of booster injections been used, it is possible that more significant differences would have emerged in the active and placebo groups. Second-generation antigens are currently in phase 2 trials [eg, CAD106 (Novartis; Clinical Trials.gov: NCT00795418) and PF-04 360 365 (Pfizer; ClinicalTrials.gov: NCT00945672)].

The approach of using preformed antibodies is also being studied (passive immunization). Passive immunity does not depend on the patient mounting an adequate immune response, and antibodies are cleared within hours of an infusion.87 Pooled human antibodies (eg, intravenous immunoglobulin, which is purified human immunoglobulin G) have been shown to contain antibodies to Aβ and possibly to Aβ oligomers as well. Recently, a small open-label study was published that followed 8 patients throughout 18 months of treatment.88 The primary outcome measure was the MMSE. Six of the 8 patients had their scores stabilize or improve at the 18-month mark. Currently, a phase 3 trial (ClinicalTrials.gov: NCT00818662) is underway with a targeted enrollment of 360 patients, and it is trying to determine if intravenous immunoglobulin significantly slows the rate of decline in patients with mild to moderate AD. The primary outcomes are the ADAS-Cog and the Clinical Global Impression of Change scores at 9 months, with a planned secondary analysis at 18 months.

It is also possible to use preformed monoclonal antibodies to Aβ. There are currently 4 phase 3 trials of bapineuzumab, 2 with apolipoprotein E4 carriers and 2 without them. Their target enrollment is over 1000 patients. The results of the 18-month phase 2 trial of 240 patients with AD did not show efficacy on the cognitive measures, but a post hoc analysis looking at patients who did not carry the apolipoprotein E4 allele showed statistically significant benefits on ADAS-Cog and the Neuropsychological Test Battery.87,89 Of note, the higher doses of the antibodies were associated with vasogenic edema, and thus the current phase 3 trial does not include the highest dosage of bapineuzumab used in phase 2.90 It is important to note that cerebral microhemorrhages have also been described even with passive immunotherapy.91

Advanced Glycation End Products

Advanced glycation end products (AGEs) are formed endogenously during glycation and can also be ingested in a variety of foods.92 These AGEs have been implicated in aging through a variety of mechanisms, including increased protein crosslinking and increased free

radical formation, and as proinflammatory mediators. Receptor for advanced glycation end products (RAGE) is an immunoglobulin super-gene family expressed on the cell surface of multiple cell types throughout the brain and on the blood-brain barrier. In AD, RAGE is up-regulated on cells in the hippocampus, such as astrocytes and microglia.93 Amyloid is known to bind to these receptors. This may be one way in which the inflammatory cascade is stimulated and thus may lead to cell death (reviewed by Chen *et al*.94). Preclinical studies have suggested that blocking this receptor against amyloid binding protects the cell by decreasing plaque formation and inflammation, and it may have an effect on memory functioning (reviewed by Chen *et al*.94). Pfizer and the Alzheimer's Disease Cooperative Study are working together on a phase 2 trial of PF-04 494 700, an oral RAGE antagonist. Recently, this dose-finding study has discontinued the highest dose because of evidence of increased behavioral disturbance and worsening cognition (ClinicalTrials.gov: NCT00566397).

Latrepirdine (Dimebon)

After the introduction of memantine, other *N*-methyl-d-aspartate antagonists were sought to expand the field of medications in this class. During one such screen, latrepirdine, once used as a nonselective antihistamine in Russia, was identified. Latrepirdine was studied in animal models of AD95 and was found to be beneficial in an avoidance conditioning paradigm. The mechanism of action of latrepirdine is unclear because it may also modulate α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid and *N*-methyl-d-aspartate receptors and weakly inhibit acheylcholinesterase.96,97 It also may act by enhancing mitochondrial function.98 Most recently, in a published trial,99 183 patients with mild to moderate AD (an MMSE score of 10–24) were given latrepirdine or placebo. At 26 weeks, the active group had improved performance on the primary cognitive outcome measure, the ADAS-Cog, as well as some secondary outcomes (including behavior, activities of daily living, and global function). In an up to 52-week blinded extension, the latrepirdine group continued to outperform on the ADAS-Cog, and the difference from placebo on the global and activities of daily living measures widened. The most common side effects were dry mouth and depressed mood, each occurring in 14% of the treated group versus 1% to 5% of the placebo group. Other adverse events [hyperhidrosis, insomnia, angina pectoris, asthenia, hyperkalemia, motor dysfunction (repetitive activity), polyuria, atrial flutter, raised blood bilirubin, dyspnea, and musculoskeletal pain] occurred at least twice as frequently in patients given Dimebon in week 26 or 52, but overall frequencies were quite low. Latrepirdine is currently in phase 3 trials in the United States.

Nerve Growth Factor

The loss of acetylcholine neurons is thought to be a significant cause of the memory loss of AD. NGF is a trophic factor for acetylcholine neurons. In a mouse model of Down syndrome, it was seen that increased APP reduced retrograde transport of NGF, and this led to the loss of cholinergic neurons.100 It is postulated that this may be a mechanism of cholinergic cell loss in AD. NGF has been shown to prevent the death of cholinergic neurons in rats in both aged and lesion models.101,102 When NGF was implanted in aging rhesus monkeys, it was demonstrated to reverse the loss of cholinergic neurons.103 In the earliest human trial, NGF was infused into the brain ventricular system of 3 patients, but it caused severe side effects, such as pain from stimulation of dorsal root ganglion nociceptive neurons, Schwann cell migration to the spinal cord, and weight loss.104 In a search for a more effective way to target NGF at appropriate areas, autologous fibroblasts were genetically modified to express human NGF and then implanted in 8 individuals with AD. There were 2 serious adverse events: the first 2 patients treated, who were sedated but were not under general anesthesia, had intraparenchymal bleeds from sudden movement. The rest of the patients were treated under general anesthesia. In this cohort, there were some

statistically significant increases in cerebral metabolism on positron emission tomography scans of several cortical regions at 6 months in 4 participants as opposed to an expected decline with disease progression.105 More recently, a phase 1 clinical trial looked at NGF in an adenovirus vector. Ten participants at Rush Medical Center and at the University of California, San Diego, were included in an open-label trial looking at various doses of NGF. The researchers continue to follow these patients.106 Again, there are what appear to be encouraging positron emission tomography findings in 4 patients (ClinicalTrials.gov: NCT00087789). Given the overall tolerability of the neurosurgical procedure under general anesthesia in the phase 1 trial, there is currently a phase 2 clinical trial (Clinical-Trials.gov: NCT00876863) using the highest dose of NGF from the phase 1 trial. The researchers are hoping to enroll 50 subjects to participate in a placebo surgery controlled trial that will look at functional, cognitive, and imaging outcomes over a 2-year period with optional extended follow-up.

Resveratrol

There has been much written about resveratrol, the component found in the skin of red grapes that, in animal studies, has a variety of anti-aging effects, including extending the lifespan of yeast and *Caenorhabditis elegans*.107,108 In mice, it seemed to improve a variety of aging outcomes (bone health, cholesterol, and coordination), but it did not increase longevity.109 In an Alzheimer's model of transgenic mice, both red wine110 and resveratrol111 significantly reduced plaque formation. Resveratrol is currently being studied in a trial at Mount Sinai with an estimated enrollment of 60 individuals (ClinicalTrials.gov: NCT00678431).

Targeting Tau

Hyperphosphorylated tau protein is the main component of the other neuropathological hallmark of AD, the neurofibrillary tangle. Some scientists argue that the development of neurofibrillary tangles is the earliest neuropathological change in AD and is correlated with disease severity.112,113 The density of neurofibrillary tangles, particularly in the entorhinal cortex, has been argued to be important in establishing a diagnosis of AD.114 Mechanistically, hyperphosphorylated tau is also known to interfere with microtubule assembly, which may promote neuronal network breakdown.115

Various avenues have been studied in animal models to address tau. One is inhibiting tau kinases,116 and others involve supporting microtubule assembly.117,118 Another avenue that has currently passed a phase 2 trial is blocking tau aggregation with methylene blue (MTC).119 MTC may also enhance mitochondrial function.120 A 24-week phase 2 trial of 321 patients with mild to moderate AD was blindly continued for up to 84 weeks. At 24 weeks, the patients on active treatment had not declined statistically from the baseline on a standard cognitive measure (the ADAS-Cog). At 50 weeks, there was an 81% reduction in the rate of decline with respect to controls, and the effect size had increased from 24 weeks. Of note, the high test dose was deemed ineffective because of crosslinking to the capsule, and the investigators decided to combine this arm with the placebo arm for statistical purposes. Another significant issue is maintenance of the blinding in this trial because MTC is known to cause the sclera and urine to turn blue.121 A larger phase 3 trial is planned.

Serotonin Receptors

The discovery of the serotonin 5-hydroxytryptamine-4 (5-HT4) receptor in the past 5 years has provided insights into the signaling pathways and the physiological roles of G protein–coupled receptors in neurons.55 Animal research has demonstrated the involvement of 5-HT4 receptors in cognitive processes, the protection of neurons via increased secretion of the soluble form of APP, and some evidence of cholinergic stimulation, and all of these are

potentially therapeutic in AD.56 Recent 2-week clinical trials in humans suggest that agonists at the 5-HT4 receptor (eg, PRX-03 140) may have a cognitive enhancing effect.57 This agent was being developed by Epix and was in a phase 2 clinical trial, but after slow enrollment and insufficient financing, the company discontinued this development and left this as an unexplored avenue. Other serotonin receptors have been or are also being explored, such as 5-HT1A (previously described xaliproden) and 5-hydroxytryptamine-6 (SB-742 457), which just underwent a phase 1 trial (ClinicalTrials.gov: NCT00551772).

CONCLUSION

This review highlights some of the approaches and directions of research in AD over the past 2 decades. Numerous pathways have been identified to be targeted for potential interventions. There have been leads from serendipitous clinical findings, from observational studies, and from the basic science efforts at the bench. Regardless of origin, rigorous clinical trials are needed to definitively prove the efficacy of any potential treatment and, importantly, to understand the true risks. In fact, this review summarizes important trials that have been successful, in that they have provided valuable information on potential treatments. Several studies with hopeful agents yielded disappointing results. For example, clinical trials with estrogen, B vitamins, and anti-inflammatory agents identified not only a lack of efficacy but also increased risk for other conditions. Thus, these studies were critically informative and provided directions for avoiding these ineffective treatments.

Over the past 20 years, we have seen the first Food and Drug Administration–approved treatments, which have been shown to have efficacy across the span of the disease, and although the effects are modest, they are consistent and replicable. The ability to answer questions about potential treatments in the next decades will require even more extensive clinical research. Specific requirements for maximizing the efficient development of preventative agents must include the identification of true surrogate markers. The markers must not only provide predictable measures of risk but also be sensitive to interventions that shift risk. Such work cannot be done without large multisite efforts with a commitment to participation in activities such as biomarker databases,122 longitudinal clinical data registries, and networks of committed subjects and practitioners who are prepared to participate in cutting-edge research. Facilitating drug discovery in AD requires building methods and infrastructure to rapidly conduct large, definitive trials.123

The recruitment of subjects to randomized clinical trials remains the great challenge and is considered the major bottleneck to drug development. It is estimated that up to 95% of the delays in study completion are attributable to difficulty in recruiting patients.124 Table 1 reviews the time and number of sites needed for some of the recent AD trials. Like the experience in cancer trials so recently articulated in the lay press,125 the regulatory processes and the protection of human subjects require resources, skill, and effort. Clinicians must not be daunted by these requirements and need to accept the challenge of educating patients about the importance of rigorously conducted research. Understanding the value of placebo control trials and the collection of important safety and efficacy information as well as sharing this knowledge with patients is a valuable contribution, particularly when this information can be delivered by trusted practitioners. Patients are eager for the assessment of practitioners about the value of research trials, and many have the altruism to make this contribution to research. A recent report from the Alzheimer's Association126 indicates that although nearly 40% of patients ask their doctor about research, only 22% of doctors raise the issue with patients and only 21% know of research in their area. This illustrates the significant opportunity that primary care providers have to contribute to the research effort. Table 2 lists the trials currently ongoing at Mount Sinai, and Table 3 provides a list of

resources for identifying research in AD both regionally and nationally. Sharing these resources can be one of the most hopeful actions that a clinician can perform for patients.

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Table 1

Clinical Trials: Duration of recruitment and number of sites.

Drug	Phase	Length	Country	Organization	Time to Recruit	Reference
Latrepiridine	2/3	6 months (blinded to 1 year), n = 183	Russia	Medivation	5 months, 11 sites	99
LY450139	2	6 weeks, n = 70	United States	Lily	8 months, 6 sites	79
Tarenflurbil	3	18 months, n = 1649	United States	Myriad	18 months, 133 sites	82*
Tramiprosate	3	18 months, n = 1052	United States	Neurochem	13 months, 67 sites	84
AN-1792	2	Terminated, n = 372	United States	Wyeth	15 months 11 sites	85*
Bapineuzumab	2	18 months, n = 240	United States	Wyeth/Elan	7 months, 26 sites	89*
Methylene blue	2	24 weeks (blinded up to 21 months), n = 321	United Kingdom and Singapore	University of Aberdeen and TauRx	Unknown, 17 sites (unregistered trial)	127
Simvastatin (CLASP)	3	18 months, n = 406	United States	ADCS	25 months, 44 sites	38
DHA (AD)	3	18 months, n = 402	United States	ADCS	5 months, 51 sites	61*
DHA (memory complaints)	3	6 months, n = 485	United States	Martek	13 months, 14 sites	61*
Homocysteine	3	18 months, n = 340	United States	ADCS	27 months, 40 sites	73

Abbreviations: AD, Alzheimer's disease; ADCS, Alzheimer's Disease Cooperative Study; CLASP, Cholesterol Lowering Agent to Slow Progression; DHA, docosahexanoic acid.

*Recruitment duration data were gleaned from ClinicalTrials.gov.

Table 2

Current Medication Trials at Mount Sinai.

Bapineuzumab
Dimebon
Intravenous immunoglobulin
Nerve growth factor
Receptor for advanced glycation end products inhibitor
Resveritrol
Risperidone discontinuation

NOTE: The general number is 212-241-8329.

Table 3

Resources to Find Clinical Trials.

Mount Sinai Alzheimer's Disease Research Center	212-241-8329	http://www.mssm.edu/psychiatry/adrc
Alzheimer's Association: national site	800-272-3900 (24-hour caregiver help line)	http://www.alz.org
Alzheimer's Disease Education and Referral Center	800-438-4380	http://www.nia.nih.gov/alzheimers
ClinicalTrials.gov	Government Web site	http://www.clinicaltrials.gov