Published in final edited form as:

Curr Neurol Neurosci Rep. 2009 September ; 9(5): 368–376.

An Update on Treatment and Prevention Strategies for Alzheimer's Disease

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Abstract

With the aging of the population, the incidence and prevalence of Alzheimer's disease will grow, increasing the burden on individuals and society. While ameliorating symptoms, the currently available treatments approved by the US Food and Drug Administration do not halt progression or cure the illness. This article discusses recent data on treatment strategies targeting amyloid and tau pathology. Novel therapeutic strategies such as inhibitors of receptors for advanced glycation end products (RAGE), potential mitochondrial modification with Dimebon, anti-inflammatory approaches, and cholesterol-lowering agents are also reviewed. An update on results from pharmacologic and nonpharmacologic prevention trials is provided.

Introduction

Alzheimer's disease (AD) will be responsible for an enormous burden on individuals and society as the population ages. The fastest growing segment of the population in the United States is the population over 85 years of age. According to the US Census Bureau, the number of individuals older than 65 will grow from about 35 million in 2000 to 70 million in 2050, and the over-85 population will increase from about 4.2 million in 2000 to 21 million in 2050. Because age is the greatest risk factor for AD, there will be a proportionate increase both in frank Alzheimer's dementia as well as individuals in the 3- to 5-year period of mild but significant cognitive impairment before diagnosis.

The medications that are available to treat AD fall into two classes, acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine, and tacrine) and *N*-methyl-D-aspartate (NMDA) antagonists (memantine). These medications do not halt the progression of the illness or reverse it. They ameliorate the symptoms and can improve functioning, but they leave the patient and the field with a great unmet need.

The field is moving forward with the development of treatments that target the known neuropathologic hall-marks of the illness, the amyloid plaques and tau-based neurofibrillary tangles. This paper discusses drugs that target amyloid and tau, the rationale for some of the most promising new agents, and both positive and negative findings in the treatment and prevention of AD.

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Disclosure

No potential conflicts of interest relevant to this article were reported.

Modulating Amyloid

The accumulation of amyloid β ($A\beta$) has been postulated as being the earliest (and possibly the inciting) factor in the development of AD. The only known genetic forms of the illness are caused by mutations in $A\beta$ or the enzymes that are involved in its formation. The amyloid precursor protein (APP) is cleaved either by a secretase into a soluble fragment (sAPP) or by β secretase (also called β -site APP-cleaving enzyme [BACE]) and then by γ secretase, which results in fragments that are 37 to 42 amino acids in length. The fragment most associated with AD pathology is $A\beta_{42}$, which oligomerizes and then further aggregates to form plaque. There is considerable interest in the oligomeric form of $A\beta$, which is toxic to neurons, contributes to memory loss in animals, and may initiate a cascade of events that contribute to activation of microglia, synaptic degeneration, oxidative injury, and apoptosis. Interventions that aim to reduce amyloid plaque burden either by altering amyloid metabolism through enzyme mediation or maximizing clearance, particularly through immunotherapy, are under study (reviewed by Barten and Albright [1]).

Immunotherapy targeted to reduce $A\beta$

There are a number of ways to attempt to reduce $A\beta$ using immunotherapy. Active immunity requires the introduction of an antigen to which antibodies are produced. In turn, the antibody binds to $A\beta$ and helps clear it from the central nervous system (CNS). Alternatively, preformed antibodies that are either specific or pooled/nonspecific can be given parenterally (passive immunization). The first trial of active immunity used an aggregated amyloid peptide (AN1792) to promote an immune response. The phase 2 trial was halted in 2002 because meningoencephalitis developed in 6% of the patients who received the vaccine. T-cell activation was blamed for this adverse effect. It is possible that this effect was enhanced by the adjuvant included with the vaccine (QS-21), which was meant to boost the immune response. Investigators continued to follow the patients who had received the vaccine, and in general the results were disappointing. Although autopsy studies showed that, in patients who mounted an antibody response to vaccination, there was a marked effect on amyloid in the brain, there were still prominent tangles, neuropil threads, and cerebral amyloid angiopathy, which is similar to what occurs in unimmunized AD [2]. There was little evidence of significant cognitive benefit as measured by the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) and Mini-Mental State Examination (MMSE), although on the Neuropsychological Test Battery a composite statistical measure did suggest some benefit. The patients continued to decline over the course of the study. For example, on a variety of global and functional measures (eg, clinical dementia rating scales, clinical global impressions, disability assessments for dementia), there was no difference between the antibody responders and placebo group. There was some suggestion of improvement on a quality-of life-measure in the patients who had an adequate antibody response [3]. One explanation for the findings of this trial is that removing $A\beta$ after years of damage is not effective, which begs the question of whether much earlier intervention (when the patient develops mild cognitive impairment [MCI] or before) might have more effect. Another explanation revolves around whether amyloid accumulation is in fact the sentinel event in the progression of AD and whether more attention should be paid, for example, to neurofibrillary tangles. A third possibility is that, had the trial been able to continue to completion, with the full course of antibody injections

and without the adverse immunologic events, the suggestion of cognitive benefit seen in the aborted trial would have become a clinically significant change in illness course. In hopes that the third explanation is valid, second-generation antigens designed to decrease the likelihood of T-cell activation are currently in phase 2 trials (eg, ACC-001 [Elan, Dublin, Ireland, and Wyeth, Collegeville, PA], CAD106 [Basel, Switzerland], and Affitope AD01 and AD02 [Affiris, Vienna, Austria]). These agents aim to induce more humoral (B-cell-mediated) immunity by using an N-terminal fragment of A β as an antigen, because it is thought that the T-cell-stimulating epitopes are more distal.

Several passive immunization trials also are under way. The benefit of passive immunity is that it does not depend on the patient mounting an adequate immune response. This may be a significant issue in the elderly, because less than 20% of the patients immunized in the AN1792 trial achieved the targeted immune response level [3]. Passive immunity is also thought to be safer, because antibodies are rapidly (within hours) cleared after an infusion [4]. Bapineuzumab (Elan and Wyeth), which is in a phase 3 trial (Table 1), is the farthest along in the process of testing. The investigators are hoping to enroll 1250 patients into this trial. In the phase 2 trial of bapineuzumab, of about 240 patients, the patients with the apolipoprotein E4 allele were at higher risk for vasogenic edema at higher doses. The efficacy measures in phase 2 did not attain statistical significance, but post hoc analyses did show statistically significant benefits in noncarriers of apolipoprotein E4 for a number of cognitive outcomes (eg, ADAS-cog and the Neuropsychological Test Battery) [4,5].

Another approach to passive immunization is using pooled antibodies (eg, intravenous immunoglobulin, which contains purified human IgG) that have been shown to contain antibodies to A β and possibly to the oligomers of A β . A recent small open-label study evaluated eight patients throughout 18 months of treatment [6]. The primary clinical outcome measures were scores on cognitive MMSE testing. Interestingly, six of the eight patients had their scores stabilize or improve at the 18-month mark. A phase 3 trial is now under way (Table 1), with a planned enrollment of 360 patients. It will evaluate two doses of intravenous immunoglobulin versus placebo to determine if it 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.

Immunotherapy, including passive immunotherapy, carries important risks. As noted, the AN1792 trial was halted due to meningoencephalitis. With the highest doses of bapineuzumab, vasogenic edema was seen in some patients, with the risk being greatest in patients with the apolipoprotein E4 allele. Thus, this dosage was removed from the current phase 3 protocol [7]. In addition, cerebral microhemorrhages have been described even with passive immunotherapy [8].

Enzyme modulators

As described above, events in the metabolism of APP may determine the likelihood of plaque formation. Inhibition of the β - or γ -secretase enzymes or enhancing α -secretase activity could result in a reduced rate of A β formation and thus amyloid plaque formation.

Perhaps the most advanced approach to enzyme manipulation in terms of clinical experience is γ -secretase inhibition. Eli Lilly (Indianapolis, IN) has completed a phase 2 study of the compound LY450139 in 51 patients that demonstrated relative tolerability and decreased plasma levels of A β [9]. Two phase 3 studies are currently recruiting, NCT00762411 (escalating dose from 60 to 140 mg/d vs placebo) and NCT00594568 (comparing 100 mg, 140 mg, and placebo) (Table 1). A phase 1 trial of MK 0752 (Merck, Whitehouse Station, NJ) has been completed, and GSI 136 (Wyeth) is being tested in Japan (Table 1). Eisai (Tokyo, Japan) had planned a phase 1 trial of E2012 in 2006 but postponed it after lenticular opacities were found in rats. After another rat and primate trial found no further evidence of toxicity, the US Food and Drug Administration (FDA) approved the phase 1 trial.

Some of the concerns about inhibiting secretases are that there may be other proteins that are involved in processing, many of which are unknown to date. For example, γ secretase is involved in the cleavage of the Notch transmembrane receptors, and chronic inhibition is associated with effects most notably in the gastrointestinal system, such as goblet cell hyperplasia (seen in animal models), diarrhea, and gastrointestinal bleeding (seen in the human trial with LY450139). Thus, toxicities must be carefully monitored with these agents, particularly novel adverse reactions from unexpected interactions.

Tarenflurbil, an anti-inflammatory agent, was found to modulate γ -secretase activity, with the suggestion of cognitive benefit in studies with transgenic mice. In a 1-year phase 2 trial with 207 patients with mild to moderate AD, it was well tolerated but did not show a beneficial effect on function or cognition. A post hoc analysis did suggest some benefit at the highest dose in the patients with the mildest disease [10]. The larger, 18-month, phase 3 trial of 1649 individuals with AD showed no benefit from treatment, and the company (Myriad, Salt Lake City, UT) stopped investigating the agent [11]. One possible explanation that was posited was that oral administration did not give high enough levels of γ -secretase inhibition to affect disease [12].

Several reports of BACE inhibitors have been described in animals, including a variety of proteins and small molecules as well as novel antibodies targeting the γ -secretase cleavage site of APP [13]. One phase 1 trial of CTS21166 (ZPQ-21166) (CoMentis, South San Francisco, CA) has been completed (Table 1).

Anti-aggregation agents

Several agents are being evaluated that block the aggregation of A β . The compound that was the furthest along in development was 3-APS, (also known as tramiprosate, homotaurine, and Alzhemed [Neurochem, Laval, Canada]). However, the phase 3 trial in the United States, which enrolled 1052 patients, was reported as inconclusive, and the phase 3 trial in Europe was halted before the data were released. The primary outcome measure was cognitive (ADAS-cog), but volumetric MRI was also performed to assess any structural disease modification effect. The FDA deemed that the US study had failed to demonstrate efficacy in the 18-month trial. The results have not been published. In an unusual strategy, the company is branding this medication as an over-the-counter nutraceutical, Vivimind. It is being marketed as protective against memory loss, due to study findings that suggested less hippocampal shrinkage in the treatment groups. Another agent, scyllo-inositol, is in

phase 2 clinical studies sponsored by Elan (Table 1). It appears to bind oligomers of A β ₄₂, preventing them from damaging synapses. The small molecule readily crosses the blood-brain barrier by active transport.

Tau-Based Therapies

The neurofibrillary tangle, composed of hyperphosphorylated tau protein, is also a hallmark pathologic finding of AD. Several studies suggest that the development of neurofibrillary tangles is the earliest neuropathologic change in AD [14,15]. Recent commentaries on the neuropathologic diagnostic criteria [16] suggest that the density of neurofibrillary tangles, particularly in the entorhinal cortex, should be considered in establishing the diagnosis. The correlation of this marker with cognition throughout the span of the disease makes it an exciting target for intervention. Hyperphosphorylated tau is also known to interfere with microtubule assembly, which may promote neuronal network breakdown.

Several mechanisms for targeting tau that have been considered include inhibitors of tau kinases [17] and agents that directly support microtubule assembly [18]. These manipulations have not been conducted in humans, but drugs that may have these mechanistic effects but have other indications in humans are being assessed in animals. An example is paclitaxel (Taxol; Bristol-Myers Squibb, New York, NY), a cell cycle-specific anticancer drug that has been associated with microtubule stabilization in cell models. This agent, or ones like it, may potentially have a benefit in AD and other tauopathies [19].

Methylene blue

Methylene blue (also known as methylthioninium chloride) is a histologic dye with a history of a variety of medical uses. It was used to treat malaria in the 19th century and is in current use for methemoglobinemia and cyanide poisoning. Under the trade name Rember (TauRx Therapeutics, Singapore), methylene blue was recently investigated as a treatment for AD because of its interference with the aggregation of tau [20] and its ability to enhance mitochondrial function [21]. The phase 2 study was an exploratory placebo-controlled trial of three doses in 321 patients with mild to moderate AD. The primary end point was the ADAS-cog score at 24 weeks, and secondary outcomes included imaging. The trial was continued, blinded, for up to 84 weeks. At 24 weeks, the patients on active treatment had not declined statistically from baseline. At 50 weeks, there was an 81% reduction in rate of decline relative to controls, with a greater effect size than at 24 weeks [22]. There were some methodologic issues (eg, the 100 mg dose was considered inert because of cross-linking with the substance in the capsule, and the data were pooled with the controls). Another issue in trials with this compound is that it causes the sclera and urine to turn blue, questioning the ability of patients and researchers to maintain a blinded study. A larger, phase 3, trial is planned.

Other Approaches to AD Treatment

Both epidemiologic and basic science data have supported the idea that several classes of agents that are in use for other indications also may be useful for AD. In this section, we explore those that have been tested in defining clinical trials.

Anti-inflammatory agents

Many lines of evidence have suggested a role of the immune system in AD, including population studies indicating that nonsteroidal anti-inflammatory or corticosteroid use lessens the risk of developing AD (reviewed by Aisen by [23]). Neuropathologic studies have demonstrated that the brains of AD patients have increased concentrations of acute-phase reactants, cytokines, and complement protein compared with aged-matched controls. However, randomized placebocontrolled clinical trials of hydroxychloroquine, rofecoxib or naproxen, and prednisone have not found benefit from these agents as treatments for AD [24–27]. For example, 351 patients with mild to moderate AD were randomized to once-daily rofecoxib (25 mg), twice-daily naproxen (220 mg per dose), or placebo [26]. The 1-year change in ADAS-cog scores in treated patients was not significantly different from scores in patients on placebo [26].

Homocysteine/B vitamins

Elevated plasma homocysteine is a risk factor for cardiovascular [28,29] and cerebrovascular [30] disease. Plasma homocysteine also has been evaluated as a risk factor for AD [31]. A study of 1092 subjects found that elevated homocysteine was an independent risk factor for AD [31], and a homocysteine level above 14 $\mu\text{mol/L}$ almost doubled the risk of AD. Homocysteine could interact with the pathophysiology of AD by potentiating $\text{A}\beta$ production or toxicity or via vascular related effects. More recently, a large 18-month prospective trial of homocysteine lowering was reported in 400 individuals with AD. Intervention did not slow cognitive decline, and there was no difference between the groups receiving the vitamins on the rate of change of a cognitive measure (ADAS-cog) in individuals with mild to moderate AD. However, the study did succeed in lowering homocysteine. [32]. Another recent study followed total homocysteine, vitamin supplementation, $\text{A}\beta_{40}$, and $\text{A}\beta_{42}$ with a high/low-dose vitamin intervention. Total homocysteine levels significantly decreased with vitamin supplementation in both groups and was strongly correlated with $\text{A}\beta_{40}$ but not $\text{A}\beta_{42}$ concentrations. There was no difference in the change in $\text{A}\beta_{40}$, $\text{A}\beta_{42}$, or the $\text{A}\beta_{42}/\text{A}\beta_{40}$ ratio over time between treatment groups. $\text{A}\beta$ measures were not associated with cognitive change. Thus, lowering the homocysteine did not actually affect the $\text{A}\beta$ levels or cognition [33].

Cholesterol-lowering agents

The story of cholesterol lowering as a method of AD treatment and prevention has taken several turns. Early basic and epidemiologic studies suggested that cholesterol lowering would inhibit beta-amyloid formation in vitro and in vivo [34]. Although some early epidemiologic studies suggested that 3-hydroxy-3-methyl-glutaryl (HMG) coenzyme A reductase inhibitors (statins) reduce the risk of AD, a meta-analysis of recent studies showed they do not exert a beneficial effect on the risk of dementia and AD [35]. Mechanisms for benefit that have been proposed include direct CNS lowering of $\text{A}\beta_{40-42}$ or other amyloid species. Simvastatin, which has reasonable CNS penetration, was associated with lowering cerebrospinal fluid (CSF) $\alpha\text{-sAPP}$ and CSF $\beta\text{-sAPP}$ after 12 weeks at a dose of 20 mg/d [36]. Notably, there was no change in CSF levels of tau, phospho-tau, or $\text{A}\beta_{42}$ or in plasma levels of $\text{A}\beta_{42}$. Similar effects were observed in asymptomatic middle-aged adults at risk for

AD; simvastatin (40 mg/d) given for up to 4 months also had no effect on CSF A β ₄₂ and tau when compared with placebo [37]. In both studies, there was a slight benefit on cognition. However, the cognitive benefit was not seen in larger trials. Atorvastatin, a non-CNS-penetrating statin, may work by creating a “sink” that encourages reduction of amyloid species in the brain. However, in one study in AD patients, a slight gradual increase in circulating A β _{1–40} and A β _{1–42} levels was produced by atorvastatin, with no significant change in levels among a placebo group [38]. The clinical and cognitive outcomes also have been disappointing. In a single-site, double-blind, placebo-controlled, randomized clinical trial in subjects with mild to moderate AD, atorvastatin had a benefit on cognitive measures when compared with placebo [39]. This benefit was more prominent in individuals with elevated cholesterol levels and higher scores on memory testing at study entry [40]. However, larger, well-controlled multicenter trials have shown no benefit in AD for simvastatin [41] or atorvastatin [34]. These results are consistent with findings from large multicenter trials of statins for the prevention of cardiovascular disease, in which no benefit on cognition or incident dementia was observed [42,43].

Estrogen

Early small open-label treatment studies suggested a positive effect of estrogen on cognition in AD. However, randomized clinical trials of the most commonly used form of estrogen, conjugated equine estrogen (CEE), in women already diagnosed with mild to moderate AD have failed to improve cognition or slow the rate of cognitive decline [44–46]. These results were consistent among studies that included progesterone [47] as well as studies that used estrogen only (in the form of CEE) [45]. Follow-up ranged from 4 to 12 months. Furthermore, there was some evidence of deleterious cognitive effects. Based on these findings, the use of CEE to treat AD in postmenopausal women is not recommended.

RAGE inhibitors

RAGE (receptor for advanced glycation end products) is an immunoglobulin supergene family expressed on the cell surface of many cell types throughout the brain and on the blood-brain barrier. In AD, RAGE has been shown to be upregulated on astrocytes and microglial cells in the hippocampus [48]. Amyloid is known to bind to these receptors, and this binding may be one of the mechanisms by which the inflammatory cascade is stimulated and may induce cell death (reviewed by Chen et al. [49]). In animal studies, blocking this receptor protects the cell against neuronal stress, plaque formation, and inflammation and may have an effect on memory functioning [49]. PF-04494700 (formerly called TTP488) is in phase 2 trials as an oral RAGE antagonist (Table 1).

Dimebon

Dimebon (Medivation, San Francisco, CA), once used as a nonselective antihistamine in Russia, was identified in a drug screen looking for NMDA antagonists. Dimebon was shown to have an effect in animal models of AD [50]. It may modulate AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and NMDA receptors and weakly inhibit acetylcholinesterase [51,52]. It also may act through a novel mechanism—that of enhancing mitochondrial function [53]. Most recently, in a trial of 183 patients with mild to moderate AD (MMSE scores 10–24), Dimebon at 20 mg three times daily improved performance in

the primary outcome measure, the ADAS-cog score, compared with placebo as well as in secondary outcomes (including behavior, activities of daily living [ADLs], and global function) at 26 weeks [54]. In a blinded extension up to 1 year, the Dimebon group continued to outperform on the ADAS-cog, and the Dimebon-placebo difference on the global and ADL measures widened. Forty-two patients (69%) were assessed on the global measure as improved or unchanged at week 52 compared with baseline. Dimebon is currently being examined in phase 3 trials in the United States.

Serotonin 5-HT4

The serotonin 5-HT4 (5-hydroxytryptamine-4) receptor identified within the past 5 years provides insights into the signaling pathways and the physiologic roles of G protein-coupled receptors in neurons [55]. Studies showing the involvement of 5-HT4 receptors in cognitive processes in animal models, protection of neurons via increased secretion of the soluble form of the APP, and some evidence of cholinergic stimulation make this a potentially interesting mechanism [56]. Recent 2-week clinical trials in humans suggest that agonists at the 5-HT4 receptor (eg, PRX-03140 [Table 1]) may have a cognitive enhancing effect [57]. This agent, developed by Epix (Lexington, MA), is now in phase 2 clinical trials.

Prevention of Dementia

There are a number of challenges inherent in defining and testing treatments for AD. The first question is when in the disease process can intervention have the greatest impact. Many have suggested that by the time a patient is diagnosed with frank dementia, it is too late to make a substantive change in the disease outcome. Thus the use of adequate pathophysiologically based treatments would be predicated on having accurate diagnostic tests that define the disease before it manifests or early enough in the course of the illness to have a significant impact. The awareness of early intervention as a model for best outcomes has spurred interest in prevention trials. Primary prevention trials are those in which interventions precede any cognitive change. Secondary prevention trials are defined here as trials in which patients have “predementia” states such as MCI, in which they have objective cognitive changes but do not meet criteria for dementia. To date, primary and secondary prevention trials have yielded negative findings. For example, primary and secondary prevention trials with nonsteroidal anti-inflammatory drugs were negative [58–60], and one recent study suggested a possible deleterious cognitive effect [61].

Trials of estrogen for preventing dementia and cognitive loss have been negative and have actually shown increased cardiovascular and dementia risk. For example, in women older than 65, the use of estrogen or estrogen/progesterone increased the odds of converting to MCI or dementia [62,63]. To what degree the presence of progesterone in hormone replacement therapy plays a role in cognition is unclear. Many biologic functions have been demonstrated for progesterone in the CNS, including modulation of inflammation, mitochondrial function, neurogenesis and regeneration, myelination, and recovery from traumatic injury. However, there is little human or clinical evidence supporting a cognitive effect. In trials of hormone replacement therapy, there is a trend toward worse cognition in replacement regimens that include progesterone [47,64] than in those that minimize progesterone [62,65]. However, none of these studies demonstrated a cognitive benefit of

progesterone in any population or trial. Although some have argued that estrogenic effects are dependent on administration within a narrow time frame, a recent randomized trial of CEE in 180 women 45 to 55 years old (< 1 year postmenopausal) identified a trend toward worsening cognition in the treated group [66]. These results make it difficult to imagine any cognitive benefit from exogenous estrogen.

Ginkgo biloba

Long touted for its healthful properties, including those on memory, ginkgo biloba was tested for a possible role in preventing all-cause dementia [67]. For a median of 6 years, this study followed more than 3000 individuals on placebo or ginkgo biloba. About 16% met criteria for MCI at the start of the trial. During the trial, participants were evaluated for incident dementia every 6 months. The rates of dementia in general, of AD in particular, and in conversion to dementia from MCI were not statistically different in the two groups. The authors did not report data on specific cognitive measures for individuals in the two groups and whether they differed, for example, on any cognitive domain.

Docosahexaenoic acid

Docosahexaenoic acid (DHA) is an omega-3 polyunsaturated fatty acid found in fish and some marine algae. Research has suggested that AD patients have lower plasma DHA levels. DHA 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. A clinical trial in Sweden found that in patients with very mild AD, omega-3 fatty acids slowed cognitive decline, as evaluated by MMSE, over a 1-year period, but no effect was seen in patients with moderate disease [68]. A current 18-month phase 3 trial is studying DHA and the progression of AD (clinicaltrials.gov identifier: NCT00440050). In addition, a recently completed trial evaluated areas of cognition and DHA in healthy elderly individuals (clinicaltrials.gov identifier: NCT00278135), but the results are still pending. Another trial, studying high- and low-dose DHA and eicosapentaenoic acid (EPA) in cognitively healthy older adults, showed no cognitive benefit over the 26 weeks of the study [69].

Nonpharmacologic Approaches

A number of nonpharmacologic approaches have been evaluated for improving cognitive functioning in the elderly. There have been a few recent randomized trials of physical activity and cognitive training. One study looked at a 6-month physical activity intervention in a randomized trial of 170 individuals age 50 and older with subjective memory complaints. The participants had to be able to perform 50 minutes of moderate activity (usually walking or other aerobic exercise) three times per week. The outcome measures included several cognitive measures, some of which showed very modest improvement over the 18-month follow-up period [70]. Another randomized study looked at the long-term effects of cognitive training of 2832 community-dwelling elderly individuals over a 5-year period. The participants underwent training sessions in memory, reasoning, or processing speed with booster sessions at 11 and 35 months. The outcome measures were self-reported measures of instrumental ADLs as well as performance-based measures of cognitive function. The performance-based measures assessed ability to reason and understand

information in everyday tasks (eg, information on medication labels, looking up a telephone number, the ability to react quickly to one of four road signs). Although this trial was not powered to detect a change in dementia incidence nor targeted at individuals with greater dementia risk, the group that received the reasoning training had fewer self-reported difficulties with instrumental ADLs at 5 years. Otherwise, the trainings were successful in improving the specific cognitive domain targeted over the 5 years of the trial. [71]. Another study looked at a different cognitive training program in 487 cognitively intact community-dwelling elderly individuals. Participants were randomized to receive a computerized cognitive training program daily for 8 weeks; the intervention did improve scores on a battery of cognitive tests, but no functional evaluations were performed [72]. Both of these trials of cognitive interventions suggest that cognitive training is possible and effective in the elderly, despite the absence of evaluations of functional outcomes and dementia risk.

Conclusions

Although it may be easy to focus on what is yet to be done to treat and prevent AD, it is worthwhile to take stock in what has been accomplished. The past two decades have seen the introduction of treatments for AD, with demonstrated efficacy for mild to severe disease. Even though the effects are modest, they are predictable, persistent, and have taught us how to conduct clinical trials for the treatment of AD. Additionally, our understanding of the molecular biology of the hallmark pathology has grown, allowing for the development of agents that target many phases of amyloid accumulation and fibrillization of tau. We are learning how to conduct trials with these agents and are developing methods for weighing safety and efficacy, including consideration of treating asymptomatic individuals who are at high risk for the disease. The development of biomarkers that may be surrogates for disease and for treatment will broaden the possibility of earlier treatment. As always, serendipity reigns supreme in drug development. The identification of the clinical efficacy of Dimebon has opened new doors to potential mechanisms and new targets. Trials in AD and other diseases may give insight into ways to improve cognition in general as well AD specifically.

At present, pharmacologic interventions that are in development offer hope for attacking targets such as amyloid accumulation. However, the promise is yet unmet because the targets need to be further refined and the crucial time frame for treatment remains uncertain. It is reasonable and wise to also examine nonpharmacologic interventions. They are perhaps less likely to yield negative effects, although only rigorous study can determine if they hold any benefit. One can envision that disease management for cognitive loss and dementia would include both behavioral change via nonpharmacologic interventions along with the most sophisticated and targeted approach to drug therapy.

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Table 1.

Drugs for Alzheimer's disease in clinical trials

Drug	Target/mechanism	Status	clinicaltrials.gov identifier
CTS21166	BACE1 inhibitor	Phase 1 completed	NCT00621010
PF-0494700 (formerly TTP488)	Blocks RAGE-amyloid interactions; reduces brain amyloid load	Phase 2	NCT00566397
LY450139	γ -secretase inhibitor	Phase 3	NCT00762411, NCT00594568
MK 0752	γ -secretase inhibitor	Phase 1 completed	NCT00803894
E2012	γ -secretase inhibitor	Awaiting phase 1	N/A
GSI 136	γ -secretase inhibitor	Phase 1	NCT00719394
Bapineuzumab	Humanized monoclonal antibody against amyloid β	Phase 3	NCT00574132
ELND005 (AZD-103 or scyllo-inositol)	Inhibits amyloid fibrillization and disassembles preformed amyloid fibrils	Phase 2	NCT00568776
Intravenous immunoglobulin	Pooled purified human IgG	Phase 3	NCT00818662
ACC-001	Second-generation active immunity	Phase 2	NCT00479557, NCT00752232, NCT00498602
CAD106	Second-generation active immunity	Phase 2	NCT00795418
Affitope AD01, AD02	Second-generation active immunity	Phase 1b	NCT00711139, NCT00711321
TRx0014 (Rember)	Tau aggregation inhibitor	Phase 2 completed	NCT00515333
PRX-03140	5-HT ₄ agonist	Phase 2	NCT00693004, NCT00672 945
Dimebon	Mitochondrial permeability transitory pore modulator; minimal cholinesterase and NMDA receptor inhibitor	Phase 3	NCT00675623

5-HT₄—5-hydroxytryptamine-4 (serotonin) receptor; BACE1— β -site amyloid precursor protein–cleaving enzyme-1; N/A—not applicable; NMDA—N-methyl-D-aspartate; RAGE—receptor for advanced glycation end products.