EXPERT REVIEWS

Early diagnosis and treatment of Alzheimer's disease

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Recently, focus on early detection, diagnosis and treatment of Alzheimer's disease (AD) has been increasing. The rationale is that, as with any other serious illness, early intervention will lead to better outcomes for patients and families. Despite the intuitive appeal of this rationale, there is discussion and even debate regarding the issues surrounding early detection and treatment. This review begins with a futuristic case that is aimed at focusing this discussion/debate and then proceeds to consider each of the issues including: should AD screening be part of routine physical examinations? is the amyloid hypothesis correct?: implications for diagnosis and treatment? can neuroimaging studies be used to detect brain amyloid? can symptomatic medications be combined to facilitate cognition? can cognitive rehabilitation programs facilitate cognition? and can immunotherapy and other plaque-busting therapies modify the progression of AD?

KEYWORDS: Alzheimer's disease • amyloid neuroimaging • cognitive • disease-modifying treatment • early diagnosis • early treatment • rehabilitation • screening • symptomatic treatment

Imagine a visit 10 years in the future by a healthy 50-year-old man to his primary care physician (PCP) for an annual physical exam. The usual procedures are performed: checking vital signs; screening for blood pressure and hypercholesterolemia; conducting a comprehensive laboratory evaluation, prostate and hernia exam, and performing an evaluation of systems. But this annual exam also includes a PET scan to image amyloid in his brain. All the annual exam procedures are within normal limits, except for the PET scan, which shows abnormally high levels of amyloid in the medial temporal cortex and to a lesser extent the parietal lobes. When the patient returns to discuss the results of his exam with his physician, he is told that the increased amyloid in his brain suggests the possibility of very early Alzheimer's disease (AD). The physician suggests that he undergo a computerized cognitive test battery that can be done in the office. The patient is seated at a computer terminal where he uses a touch screen to answer a series of questions about his cognition, and then undergoes a series of tests to evaluate various areas of cognition including memory, praxis, visuospatial function, language and executive function. At the completion of the evaluation, a report is generated for the physician. When the patient again meets with the physician, he is told that the tests suggest that he is experiencing some very mild cognitive deficits. The physician indicates that these deficits may be the very earliest signs of AD. He explains to the patient that AD is a brain disease in which very slowly, but very surely, brain cells die. He further explains that as these brain cells die, cognitive abilities are lost. He also explains that the loss of brain cells in AD is due to the production of an abnormal brain protein called β-amyloid (Aβ) and that this Aβ was what was detected on the PET scan. He then assures the patient that because the disease has been detected at the very earliest stages, excellent treatments exist that should both be able to remediate some of his cognitive deficits and prevent the further progression of the disease. The physician suggests a threefold approach to treatment:

- A combination of medications that boost the level of chemicals in the brain, which allow brain cells to communicate and, in doing so, improve memory and related cognitive functions.
- A series of cognitive exercises that will further improve cognitive function and allow him to build cognitive reserve.
- Vaccinations that will both clear existing amyloid plaques and prevent formation of new plaques.

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This case raises a number of issues that may help focus the debate on how to diagnose and treat early AD. These issues include:

- Should AD screening be part of routine physical examinations?
- Is the amyloid hypothesis correct?: implications for diagnosis and treatment.
- Can neuroimaging studies be used to detect brain amyloid?
- Can symptomatic medications be combined to facilitate cognition?
- Can cognitive rehabilitation programs facilitate cognition?
- Can immunotherapy and other plaque-busting therapies modify the progression of AD?

Should screening be part of routine physical examinations?

Dementia is a syndrome characterized by deterioration of previously acquired intellectual abilities that interferes with social or occupational functioning. A major health problem, dementia will have an increasingly significant economic and social impact on the USA. The primary factor associated with the rising prevalence of dementia is the aging of the American population.

Dementia will develop in 5–11% of all people over the age of 65 years, and it will affect as many as 50% of those over age 85 years, the fastest growing segment of our population. In the elderly, the most common cause of dementia is AD, with an estimated US prevalence of 5.5 million cases. By the year 2040, there may be 16 million people with AD in the USA and 80 million worldwide [1]. The prevalence and incidence of dementia double every 5 years in individuals between the ages of 65 and 95 years. The fourth leading cause of death (after heart disease, cancer and stroke), AD accounts for more than 100,000 deaths a year, and the costs of caring for AD patients are estimated to be approximately US$110 billion annually.

Yet, despite the increasing prevalence of AD, the enormous emotional and financial costs, and the emerging treatments for the disease, AD continues to be underdiagnosed. By some estimates, fewer than half of all AD patients are currently diagnosed [2–5], and only approximately 25% are treated with antidementia compounds [6].

One strategy that has been proposed to help combat underdiagnosis of AD is routine screening in the elderly. There has been a rapid proliferation in both screening initiatives and screening instruments over the past 10 years. A number of groups have advocated routine screening. The goal is to make screening for cognitive impairment as routine as screening for hypertension, hypercholesterolemia, or prostate or breast cancer. While this approach appears obvious, it is not without its critics and has met with resistance owing to both pragmatic and theoretical issues. We have previously reviewed the arguments both for and against routine screening in both primary care practices and within the community [7].

Arguments for screening

Underdiagnosis of AD

AD is particularly underdiagnosed in primary care settings, perhaps because patients with early AD often appear entirely appropriate in the context of a brief office visit [3,8,9]. By some estimates, up to 95% of cases of mild dementia are not detected by clinicians [10]. In one small study, 78.6% of patients with mild dementia, 71.4% with moderate dementia and 20% with severe dementia had no indication of cognitive deficits in their medical records [4]. Other studies in primary care practices have found rates of undetected dementia between 50 and 66% [2,4].

Implementation of social support systems

Implementation of social support systems to address issues of care, nutrition and safety, as well as financial and legal planning, will also be most beneficial when initiated early in the course of a progressive disease. For example, patients with AD have increased risk for automobile accidents [11]; they also mismanage comorbid illnesses, including not accurately reporting symptoms of these illnesses [12] and, consequently, more healthcare dollars are spent to manage these conditions [13,14]. Early screening and diagnosis of AD would allow patients and families to make decisions regarding transportation, living arrangements and other aspects of care when the patient is functioning at the highest possible level.

Benefits of early treatment

Treatment with cholinesterase inhibitors may be of greatest benefit when initiated early in the disease; there is evidence that early treatment may help maintain individuals at a milder and less costly disease state [15]. Early treatment may also delay milestones such as nursing home placement, resulting in social and economic benefits to the patient and family.

Arguments against screening

The US Preventative Services Task Force Position

The US Preventative Services Task Force evaluated screening for AD in 1996 and 2003. As in the 1996 report, the most recent report, did not endorse routine screening for AD [16]. Although they raise a number of concerns regarding screening for AD, including a low prevalence of AD, insufficient evidence of the accuracy of screening tests, low accuracy of screening tests for mild dementia, and biases for age, education and ethnicity, the primary rationale of the Preventative Services Task Force for not endorsing screening is that until there are studies that demonstrate screening (and by implication, earlier diagnosis) provides better outcomes for patients with AD, endorsement is premature. The task force did, however, recognize the potential importance of screening and suggested that screening to detect dementia at an early stage is desirable because only early intervention can modify an otherwise certain decline. But rather than endorsing screening, they endorsed further research in screening for dementia. Other groups have supported similar positions [17].

Table 1. The debate regarding screening in primary care practice.

Brayne *et al.* criticisms	Alternative view points
Screening tests: although existing instruments have good sensitivity and specificity, the positive predictive values are low.	Positive predictive values can be improved by enriching the screening sample. Recent guidelines (Cummings *et al.* [20]; Fillit *et al.* [21]) address this by recommending frequency of screening as a function of age, risk factors and cognitive complaints. For example, one set of guidelines suggests discretionary screening from age 65 to 74 years (prevalence = 3%), based on family history and cognitive complaints from the family or patient; from age 75 to 84 years (prevalence = 19%), every 2 years or if there are complaints from the family or patient; and >85 years (prevalence = 47%) annually.
Treatments: disease-modifying drugs that may only be beneficial if the disease can be modified before the onset of symptoms.	There are multiple potentially disease-modifying treatments in clinical trials. For example, Flurizan™ has positive Phase II data and Phase III results will be available over the next few months. Bapineuzumab (passive vaccination) will present Phase II results in early 2008 and Elan has already decided to implement a Phase III trial. Several companies are pursuing trials with secretase inhibitors. It is self apparent that in the treatment of a neurodegenerative disease intervention at the earliest possible stage will be most beneficial.
Screening programs: patients may refuse follow-up care after a positive screen because of fear of loss of driving privileges or denial of long-term care insurance.	Unfortunately, denial of long-term care insurance is already taking place because some insurance companies routinely screen applicants for cognitive deficits. Similarly, several states are now considering screening elderly drivers. The question then becomes not whether broad-based screening will come about, but who will conduct the screening.
Limited evidence: there have been no large-scale randomized controlled trials demonstrating the benefits of screening.	Absence of proof is not proof of absence. Interestingly, although the most recent US Preventive Services Task Force report (2003) did not recommend broad-based screening, it did recognize that screening to detect dementia at an early stage is desirable because only intervention at an early stage can modify an otherwise certain decline.

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More recently, a commentary in the *Journal of the American Medical Association* by Boustani and colleagues reviewed the arguments against routine screening in primary care practice [18]. Both these arguments and counterarguments are summarized in Table 1 [19].

The debate of whether or not to screen in primary care practices is likely to continue. Nevertheless, screening appears to be occurring with greater frequency. Several groups are now actively advocating both for routine screening by PCPs as well as for large-scale community screening. For example, Rabins, Cummings and Relkin [20] have suggested screening can be considered a brain check-up and Fillit *et al.* [21] recommended screening as part of best practices for the treatment of AD in managed care. Both groups suggest screening paradigms based on a combination of risk factors including age [20,21], as initially suggested by Solomon and Murphy in 2005 (Table 2) [7]. Other groups, including the Alzheimer's Foundation and the recently formed AD Screening Discussion Group (2002) [22], have also advocated for routine screening. There is also support for making cognitive screening part of the Welcome to Medicare Package.

All groups who advocate screening recognize the important distinction between screening and diagnosis, and emphasize that positive screening results should lead to comprehensive diagnostic evaluations and not diagnosis.

Is the amyloid hypothesis correct?: implications for diagnosis & treatment

The amyloid cascade hypothesis starts with the premise that the primary culprit in the pathogenesis of AD is the accumulation of toxic forms of amyloid. It then follows that the focus of disease-modifying treatments is on drugs that either affect amyloid directly, the so-called plaque busters, or drugs that affect the downstream consequences of amyloid, such as inflammation, oxidative stress and neurofibrillary tangle (NFT) accumulation. It also follows that if amyloid accumulation is one of the earliest signs of AD, then early diagnosis may be facilitated by techniques (e.g., imaging) aimed at identifying amyloid early in the progression of the disease, and perhaps even before symptoms emerge.

Table 2. Summary recommendations for screening of cognitive impairment.

Age (years)	Prevalence (%)	Recommendation
65–74	3	Discretionary, driven by signs of cognitive impairment noted by either patients or caregivers
75–84	19	Screening should be performed annually or biannually, or whenever the presence of cognitive impairment is noted
≥85	47	Annually for all patients

See reference [7].

The amyloid hypothesis also makes the assumption that amyloid is being deposited in the brain for many years before the symptoms of dementia emerge, perhaps as early as age 40 years [23]. It follows that neuroimaging for brain amyloid may be one method to detect the earliest signs of AD.

According to the amyloid cascade hypothesis, the initial assumption is that different gene defects can lead, either directly or indirectly, to an increase in toxic forms of amyloid (Aβ). The increase may either be due to overproduction of, or failure to clear, toxic forms of amyloid. Gradual accumulation of aggregated Aβ leads to a multistep cascade that includes gliosis, inflammation, neuritic and synaptic changes, NFTs and neural transmitter loss, ultimately resulting in dementia.

β-amyloid is a small piece of a much larger protein called amyloid precursor protein (APP). APP is a transmembrane protein that, when activated, is cut into smaller segments that operate either inside or outside the neuron. There are several ways that APP can be cut, and one of these leads to Aβ.

There is substantial evidence to support the amyloid cascade hypothesis including [24]:

- AD patients have amyloid plaque counts that far exceed those found in normal aging.
- The amount of amyloid found in portions of the brain involved in cognition increase with age and are correlated with the degree of cognitive impairment.
- Down's syndrome patients, who invariably develop AD pathology by age 50 years, produce too much Aβ from birth.
- Aβ fibrils damage neurons in culture and activate brain inflammatory cells (microglia).
- In a few hundred extended families worldwide, researchers have discovered genetic mutations that either increase Aβ production or deposition; the incidence of AD in these families is significantly higher than the incidence in the general population.

Although the amyloid hypothesis is the most widely accepted hypothesis of AD, it is certainly not universally accepted. For example, some researchers have proposed that NFTs may in and of themselves produce neuronal damage. Moreover, there is debate about the relationship between amyloid deposition and the degree of cognitive decline [25].

Can neuroimaging studies be used to detect brain amyloid?

In response to the amyloid cascade hypothesis, there is now considerable interest in developing techniques to image brain amyloid. PET imaging using ligands that bind to amyloid is being investigated as a technique to diagnose AD and to track disease progression. The best characterized ligand is Pittsburgh Compound B (PIB) that has the ability to bind to amyloid in living AD patients [26]. Initial data have shown that the ligand is present in:

- The same areas of the frontal, parietal and temporal cortex that show postmortem deposition of amyloid plaque in patients with AD [27].
- The same areas of the frontal, parietal and temporal cortex that show decreases in fluorodeoxyglucose-PET [27].
- The brains of patients with mild cognitive impairment (MCI), suggesting a methodology for earlier diagnosis.
- The brains of approximately 20% of cognitively normal older subjects, indicating that they may have amyloid plaque accumulation suggestive of presymptomatic AD.

One potential limitation of PIB for community-based screening or therapeutic evaluation is the short half-life (20 min) of the compounds. More recently, other ligands have been developed that may be both amenable to PET and SPECT imaging and have considerably longer half-lives than PIB, raising the possibility of more widespread use. For example, Avid Radiopharmaceuticals is evaluating a family of compounds that may image amyloid, have half-lives of up to 13 h, and may be amenable to both PET and more broadly available SPECT scans [28].

It is noteworthy that a recently proposed revision of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) guidelines for the diagnosis of AD suggest diagnosis if there is the presence of core features that include progressive changes in memory function over more than 6 months and one or more supportive features that include specific patterns on functional neuroimaging with PET including reduced glucose metabolism in the temporal parietal regions and/or other well validated ligands (e.g., PIB) [29]. The goal of these revised guidelines is to move diagnosis and treatment earlier in the progression of the disease [30].

Can symptomatic medications be combined to facilitate cognition?

Symptomatic drugs are designed to delay the progression of symptoms with the goal of preserving functional ability so that the patient remains at a particular stage of disease for as long as possible. There is, however, no evidence that any symptomatic medications delay the progression of neurodegeneration.

The US FDA has approved two general classes of drugs for symptomatic treatment of AD: acetylcholinesterase inhibitors (ChEIs), including tacrine, donepezil, rivastigmine and galantamine, and NMDA antagonists, specifically memantine. Evidence for the safety and efficacy of these drugs in treating AD in the mild-to-moderate stages comes from a large number of double-blind, placebo controlled trials [31]. Recently, the FDA has also approved donepezil for late-stage AD [32]. Based upon these data, many clinicians routinely prescribe a trial on a ChEI and/or memantine for patients with AD.

Trials with ChEIs suggest similar efficacy among drugs, although relatively few head-to-head trials have been conducted. Two of these studies have compared donepezil against

rivastigmine, and two have compared donepezil versus galantamine. However, based upon these studies, each of which has methodological limitations, no conclusive statements about comparative efficacy can be made [33]. Similarly, there are no data to support switching from one cholinesterase inhibitor to another, although this is sometimes done clinically in an attempt to reduce side effects and improve tolerability or to enhance efficacy.

Memantine is a noncompetitive NMDA receptor antagonist that is approved by the FDA for moderate-to-severe AD. Although there is some evidence to support the efficacy of memantine in mild stages of AD, the data are equivocal and memantine has not been approved by the FDA for treatment of early-stage AD. In moderate-to-severe AD patients, there is evidence to suggest that when memantine is combined with donepezil there is benefit beyond that of donepezil alone. As such, many patients in the moderate to later disease stages combine these medications [34].

There is now considerable ongoing research evaluating symptomatic drugs to treat AD. The rationale for this research is that there are multiple transmitter systems that are adversely affected by AD, and as such it may be possible to positively affect symptoms with a cocktail of drugs that enhance multiple transmitter systems. The combination of ChEIs and memantine is the first step, but other symptomatic drugs are currently being evaluated either alone or in combination with ChEIs. These symptomatic treatment drugs include serotonergic agonists, nicotinic agonists, dopminergic agonists, inverse GABA agonists, norepinephrine agonists, inverse histamine agonists, somatostatin agonists and others. There is also the prospect that a cocktail of symptomatic drugs will be combined with disease-modifying drugs to treat AD. This is already ongoing in the context of clinical trials. The vast majority of clinical trials evaluating disease-modifying drugs allow patients in these trials to remain on their current AD medications (cholinesterase inhibitors and/or memantine). This treatment regimen may well presage clinical treatment.

Can cognitive rehabilitation programs facilitate cognition?

The proliferation of commercially available cognitive-enhancing programs to facilitate attention, memory and related function has raised many questions about the efficacy of this approach. Perhaps the most widely used program is Nintendo's 'Brain Age' which is run on the company's hand held unit (Nintendo DS). This program claims to lower the user's 'brain age' by engaging the participant in a series of daily exercises. Most other cognitive-enhancing programs are also computer based and make similar claims of improved cognition following regular use.

Although these programs claim to enhance cognitive function, there is currently little empirical evidence to support these claims. For example, Nintendo's brain age is based on initial work in patients with dementia [35], but there is no empirical support for the claims of lowering brain age in cognitively intact adults. A second widely used program, 'Brain Fitness' (Posit Science), recently released results from a company sponsored trial; the company claims that elderly (mean age 71 years) participants who trained on the Brain Fitness program for 8 weeks had better cognition than a nontrained control group [36], Posit Science currently has a large-scale trial underway to further evaluate this technology.

Ultimately, these programs will need to demonstrate their benefits using the same standards as pharmacological studies [37]. Specifically, they will need to demonstrate clinically significant benefits for participants on both objective cognitive tests and on global measures of function. Moreover, outcome studies will need to demonstrate that the cognitive benefits derived from the cognitive enhancing programs generalize to neuropsychological tests (tests that are not part of the training regimen to control for practice effects), as well as to day-to-day activities. Interestingly, Willis *et al.* have recently reported the results of a multicenter trial in which older (>65 years) participants given access to ten exercises designed to sharpen reasoning abilities were better than controls 5 years post training in their ability to perform daily tasks of independent living, suggesting that these benefits may both persist and generalize [38].

Can immunotherapy & other plaque-busting therapies modify the progression of Alzheimer's disease?

Perhaps the single best argument for the early detection and treatment of AD is the emergence of disease-modifying medications; these treatments may slow, and perhaps eventually even halt, neuronal loss. Although there are a number of approaches to developing these disease-modifying treatments, directly affecting the amyloid plaque is the approach that has attracted the most interest.

There are multiple drugs currently in clinical trials that are being evaluated for their ability to alter amyloid production or aggregation, and other drugs that may clear brain amyloid [39]. Other disease-modifying drugs are aimed at the downstream effects of the plaques (Figure 1).

Plaque busters

Although these drugs can act in a variety of ways, they are all designed to affect the amyloid plaque.

Active immunotherapy

The strategy used by these compounds is to mobilize the immune system to produce antibodies to recognize and attack Aβ. To accomplish this patients are injected with live $A\beta_{1–42}$ or a fragment of $A\beta_{1–42}$.

Initial studies in mice that were genetically engineered to produce toxic forms of amyloid, and experienced difficulty in learning mazes, and other learning and memory tasks benefited from being vaccinated. Vaccinated mice had fewer plaques than nonvaccinated mice, and they showed enhanced learning and memory [40].

The first large scale clinical trial in humans with AD was with live amyloid (βAP_{1-42}, Elan compound AN 1792) or a placebo infused into volunteers. The trial received enormous publicity and was enrolled quickly with 300 volunteers with AD. The trial, however, was stopped prematurely because of brain inflammation in approximately 6% of patients. Some of the patients in the study have been followed since their vaccinations in 1999. Several patients, who died from other medical reasons, have come to autopsy; the autopsy results indicated substantially less plaque in the brain of patients from the study who have received active vaccine as compared with the brains of the patients who received placebo. Additionally, some of these patients were followed at 1 year and 4.5 years after vaccination. At 1 year, vaccinated antibody responders (those with increased titers) performed better on a cognitive test battery [41]. A subset of these patients (n = 17) were evaluated again 4.5 years after their initial vaccination. These 17 patients continued to show increased Aβ titers compared with placebo controls. Additionally, compared with placebo controls, the vaccinated patients showed significantly less functional decline on measures of activities of daily living and dependence on a caregiver. These patients also did not show any additional episodes of brain inflammation (encephalitis) [42].

There are currently several trials ongoing with active vaccine from Elan and Wyeth pharmaceuticals. There are also planned or ongoing trials with active vaccines from Merck and Lilly.

Passive immunotherapy

The strategy employed is to administer laboratory-produced antibodies to $A\beta_{1-42}$ to humans. The rationale is that an AD vaccine might be safer if the laboratory-produced antibodies are administered instead of mobilizing the AD patient's immune system to produce antibodies. To accomplish this, antibodies are produced in mice. The antibodies are then genetically engineered or humanized to be suitable for humans and then infused in patients. Laboratory-produced antibodies can be given like any other drug in fixed doses and, unlike a live vaccine, do not persist in the body after the dosing stops. The benefit to using laboratory-produced antibodies is that it is possible to halt treatment in the presence of side effects. However, this approach will require regular infusions/injections of the antibody.

Several companies are developing laboratory engineered anti-Aβ antibodies that are delivered directly to the patient. Elan and Wyeth pharmaceuticals have recently completed a Phase II study testing multiple doses of humanized monoclonal anti-Aβ antibodies (bapineuzumab) in approximately 240 patients with AD. In this study, groups of patients were given varying doses of either the anti-$A\beta_{1-42}$ antibodies or a placebo for an 18-month period. During this time, they periodically underwent both cognitive testing and volumetric MRI. The data from this study should be available in the next few months.

Even though the Phase II trial is not as yet complete, Elan and Wyeth have begun a Phase III trial of bapineuzumab. The trial that began in early 2008, will enroll approximately 2000 patients. The unusual step of beginning a Phase III trial before the completion of the Phase II trial was based in part on planned interim analysis of the Phase II trial. A parallel trial is also planned outside the USA. Bapineuzumab has been fast-tracked by the FDA.

Blocking the formation of Aβ

β-amyloid is cleaved from the larger APP by the action of secretases. It is generally believed that certain forms of Aβ ($A\beta_{1-42}$) are more toxic than other forms. This rationale informs the strategy of developing drugs that will discourage the formation of $A\beta_{1-42}$.

In normal APP processing, APP is cut by α-secretase and γ-secretases to form soluble and harmless fragments. However, in abnormal processing, APP is cut by β- and γ-secretase to form $A\beta_{1-42}$. This raises the possibility of inhibiting the formation of $A\beta_{1-42}$ with a class of drugs called secretase inhibitors. There are a number of secretase inhibitors in development, but development is challenging because of target based toxicities due to effects on other secretase substrates such as Notch. Nevertheless, because of the potential of this approach, it is likely that this class of drug will be evaluated in AD patients. To date, the results of early Phase I trials have been reported [43,44].

Another, and potentially less toxic, approach to lowering levels of $A\beta_{1-42}$ is through the use of a selective βAP_{1-42}-low-

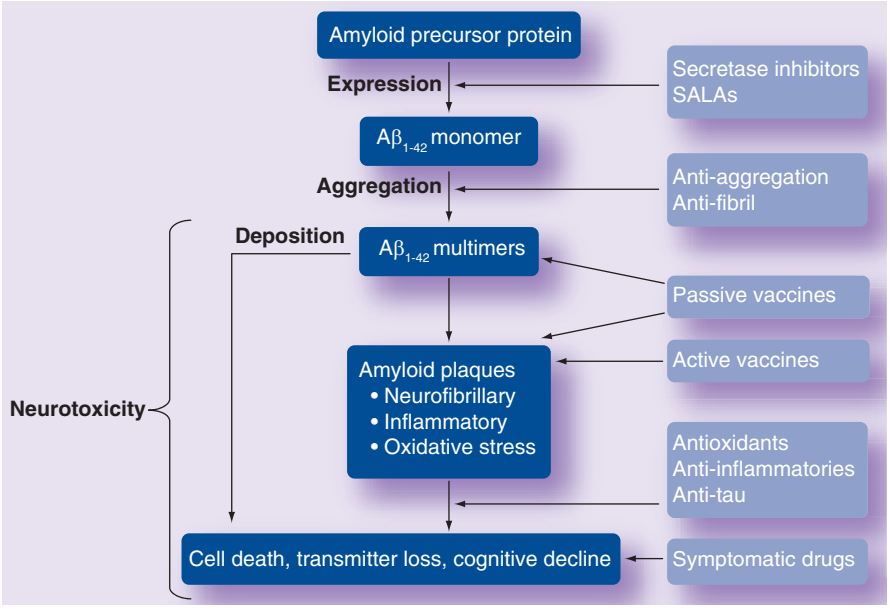

Figure 1. Downstream effects of the plaques.

ering agent. R-flurbiprofen (Flurizan™) is one example of this type of drug. A Phase II study in which patients took 1600 mg/day of Flurizan demonstrated significant positive effects as measured by both assessments of global function (Clinical Dementia Rating [CDR]) and objective cognitive tests (Alzheimer's Disease Assessment Scale-cognitive subscale [ADAS-cog]). Additionally, a meaningful number of patients experienced no decline over a 2-year period. The results of two Phase III trials of Flurizan will be available later this year.

Blocking accumulation of Aβ

Because Aβ exists in many forms in the human brain, one important question is: which form is most toxic? Aβ is initially cleaved and forms single pieces or monomers. The monomers are soluble and are not believed to be toxic. It is hypothesized that the monomers then combine into clusters to form Aβ oligomers, and finally the oligomers form insoluble fibrils also known as β-sheets. Collectively, these processes are known as aggregation. The β-sheets further accumulate and become deposited as senile plaques [45]. It is not clear how long this entire process takes, but some researchers hypothesize that it occurs over many years or decades [46].

In order to develop interventions, it is important to fully understand the amyloid cascade. For example, if the Aβ does not become toxic until the stage of insoluble β-sheets, then interventions that block this stage could be therapeutic. The first drug believed to block the creation of insoluble β-sheets that has been tested in patients is tramiprosate (Alzhemed®; 3-amino-1propanosulfonic acid) in development by the Canadian pharmaceutical company, Neurochem. Alzhemed binds to soluble Aβ and in doing so is hypothesized to block the chain of events leading to the formation of toxic β-sheets. Studies in cell culture and in animals lend support to this hypothesis.

In a Phase II clinical trial, 58 AD patients were randomized to receive either placebo or one of three doses of Alzhemed over a 3-month double-blind period [47]. The results of the study indicated that the drug was generally safe and well tolerated. Results of lumbar punctures also showed that there was a reduction of Aβ in cerebrospinal fluid. There were no differences in cognitive tests over the 3-month period, but it is important to note that the study was not designed (it was too short in duration) to allow detection of cognitive differences. The results of a recent Phase III study, however, appear negative, although there were mean differences between drug and placebo groups [101].

Another approach to preventing the aggregation of amyloid involves clearing less harmful forms of amyloid before they aggregate. One potential method to accomplish this is through the use of cholesterol lowering drugs. Retrospective studies of individuals who took cholesterol lowering drugs (statins), typically for hypercholesterolemia, have a significantly lower risk of having AD [48]. Data from randomized prospective studies are lacking, but results from a randomized controlled trial conducted by the AD Cooperative Study (ADCS) comparing simvastatin to placebo is now complete, and preliminary analysis of the results indicates no beneficial effects of simvastatin on cognitive or clinical assessments [Sano M; Pers. Comm., 2008].

Downstream approaches

According to the amyloid cascade hypothesis, amyloid plaques lead to neuronal death through a variety of mechanisms including inflammation and oxidative stress. If this is the case, then anti-inflammatories and antioxidants could be neuroprotective.

Anti-inflammatories

The Baltimore Longitudinal Study of Aging has followed volunteers since 1958. Retrospective analysis found that individuals taking NSAIDs for more than 2 years as compared to aspirin or acetaminophen were much less likely to develop AD. Other retrospective studies provided similar results [49]. The hypothesis put forth to explain this finding was that amyloid plaques could cause neuroinflammation, which could injure neurons. Unfortunately, randomized prospective studies have not supported the use of anti-inflammatories to treat patients with AD. The ADCS conducted a study in which patients were randomized to receive a COX-2 inhibitor (rofecoxib) or a non-specific NSAID (naproxen) or a placebo. Patients with mild-to-moderate disease took daily doses of the assigned drug for 1 year. The results indicated that there was no change in the rate of cognitive decline in those taking rofecoxib or naproxen compared with placebo [50]. It is possible that these drugs need to be administered much earlier in the disease process.

Vitamin E

Sano *et al.* reported the results of a large, double-blind, placebo controlled, randomized trial demonstrating beneficial effects of high doses (2000 IU/day) of vitamin E in patients with mild-to-moderate AD [51]. Vitamin E-treated patients, compared with placebo, reached milestones in AD, such as loss of an important activity or placement in a nursing home, later than placebo-treated patients. Additionally, vitamin E was well tolerated and without significant reported side effects. To date, this is the only randomized trial in patients. Nonetheless, based upon the results of this study, many patients with AD started taking high doses of vitamin E and it has become widespread practice for people concerned with developing AD, for example patients with MCI, to take vitamin E.

Although there have been no subsequent randomized studies with vitamin E in AD patients, there have been other studies that bear the use of vitamin E in patients with AD. A recently completed large double-blind, placebo controlled study evaluated vitamin E versus placebo and Aricept® in patients diagnosed with MCI; the study results did not demonstrate vitamin E to be beneficial. The primary outcome measured in the study was whether individuals with MCI would progress to AD over a 3-year period. Vitamin E showed no difference compared with placebo [52]. Another study evaluated the cardiovascular benefit

of vitamin E and found that not only was there no benefit, but the data suggested that there may be increased risk of heart failure in patients with diabetes or vascular disease. A meta-analysis of vitamin E trials, although criticized for its methodology, reported an increase in deaths [53]. To summarize, there is only one randomized trial that showed benefit with little risk in patients with AD. At present, there is no evidence that vitamin E can prevent AD in cognitively healthy patients or those with MCI. Moreover, vitamin E may increase the cardiac risk in individuals with vascular disease or diabetes.

Ginkgo biloba

Ginkgo is purported to have antioxidant properties and to enhance memory. A study of Ginkgo in AD patients published in the *Journal of the American Medical Association* in 1997 was portrayed by the media as showing benefit in patients with AD [54]. More careful scrutiny of the study, however, suggests minimal benefit for AD patients. Although a direct comparison can only be made in a head-to-head trial, the benefits of Ginkgo appear to be much less than the benefit seen with approved medications. Since then, there have been other randomized trials of Ginkgo that have not shown any benefit in AD patients. Additionally, a placebo controlled, double-blind, randomized trial in healthy elderly also showed no benefit for ginkgo [55].

Docosahexaenoic acid (fish oil)

Recently, there has been considerable interest in the potential beneficial effects on cognition of docosahexaenoic acid (DHA), an omega-3 polyunsaturate that is found in fish oil. In a recent study, researchers followed 899 men and women over a 9-year period as part of the Framingham heart study [56]. During this time, 71 of the volunteers developed AD. However, people with the highest levels of DHA in their blood had a 39% lower risk of developing AD. People in the Framingham study who had the highest DHA levels reported that they ate two to three servings of fish per week, much more than those with lower DHA levels. Fatty fish such as mackerel, lake trout, herring, sardines, albacore tuna and salmon are high in DHA. The ADCS is currently conducting a prospective, randomized trial to determine if DHA can slow the progression of AD. The results should be available over the next few years.

Summary & alternative perspectives

In this review, we have attempted to take a progressive view of the future of the diagnosis and treatment of AD. In doing so we have suggested that:

- Although controversial, routine screening for AD is feasible and the potential benefits to the patient, including access to medication and implementation of social support systems, may well outweigh the perceived risks. We suggest there are now screening instruments that have both high sensitivity and specificity that can be administered in a variety of settings including primary care practices.
- If the amyloid cascade hypothesis is at least partially correct, the view that abnormal deposits of toxic forms of amyloid informs hypotheses regarding both the early diagnosis and early treatment of AD.
- Early diagnosis may be facilitated by the use of PET and SPECT imaging techniques. There are currently ligands (e.g., PIB) that appear to bind to amyloid, as well as other compounds that are earlier in development which may be more amenable to routine clinical use.
- There are currently four symptomatic drugs approved for the treatment of AD. These drugs delay the progression of symptoms with the goal of preserving functional ability so that the patient remains in a particular stage of disease for the longest possible time. They do not, however, slow neurodegeneration. There are also multiple symptomatic drugs in various stages of development. We suggest that there may ultimately be a cocktail of symptomatic drugs for AD patients. Moreover, this cocktail could be individually tailored to the patient based upon pharmacogenomics and the nature of their cognitive deficits.
- Cognitive rehabilitation programs are only beginning to be used to treat cognitive deficits in AD patients. Despite claims of efficacy, there are few data to support these claims. Nevertheless, we suggest that there is potential for this approach and further suggest that each of these programs needs to be evaluated with same experimental rigor as programs to evaluate the efficacy of pharmaceuticals.
- The primary focus of current research in AD treatment is on disease-modifying drugs. The goal of this approach is to slow and ultimately halt the progression of AD. The focus of this approach has been on amyloid production, aggregation and clearance. There has also been work on the downstream effects of amyloid plaques including NFTs, oxidative stress and inflammation.
- We have suggested that we can envision a time when AD will be diagnosed early (and perhaps prior to symptoms) through a combination of biomarkers and cognitive screening. We further envision that the disease will be treated with a combination of symptomatic drugs, disease-modifying treatments and cognitive rehabilitation. We have further suggested that this combination of early diagnosis and treatment could lead to successful management of this difficult disease.

As noted, the above points represent a progressive and perhaps overly optimistic approach. What we are really presenting is a roadmap for eventual successful management. This roadmap, however, has numerous potential potholes and detours along the way including:

- Widespread screening may not produce the desired results. It is possible that the result of trials where patients are randomized to be screened or not screened will not show any additional benefit in terms of coping with the disease for patients in the screening condition.

- Early identification via imaging studies and other biomarkers continues to be challenging. For example, data from the Elan vaccine studies on AN1792 [57], using volumetric MRI found a decrease in neural volume in vaccinated patients as compared with controls as opposed to the predicted increase. The *post hoc* explanation of this finding is that the tissue loss in vaccinated AD patients was due to a loss of amyloid.
- Combinations of symptomatic drugs may be no more efficacious than current medications. Although there are numerous studies to support the efficacy of cholinesterase inhibitors, there are those who continue to suggest no demonstrable efficacy for this class of drugs. Moreover, there is little current evidence to suggest that combining symptomatic drugs provides any additional benefit.
- The current group of disease-modifying drugs now in clinical trials may not be efficacious and/or safe. For example, despite enthusiasm about tramiprosate (Alzhemed) and encouraging Phase II data, the data from the Phase III trial, although not as yet fully disclosed, appear negative. The AD community has carefully monitored the results of this study because this was the first study with a disease-modifying drug that might have been submitted to the FDA for consideration. This study has also raised the specter that the design of Phase III trials for disease-modifying drugs may be problematic. For example, the length (up to 18 months vs 3–6 months for symptomatic drugs) and number of subjects (300–500 vs 1000–2000) necessitate a significant and substantial increase in the number of sites necessary to conduct these studies (100–200 vs <100), raising the possibility of less experienced sites participating in studies with complex outcome measures and in turn leading to increased site-to-site variability. It is also possible, although unlikely, that the amyloid hypothesis may be incorrect or that the initiating pathogenic events in AD may occur so early in the disease process that the events that are now being pharmacologically targeted may not affect the clinical symptoms (Figure 1) [45].

Expert commentary & five-year view

AD is a devastating neurodegenerative disease for patients, their families and society. The difficulty of managing this disease for all concerned will grow dramatically over the next 30–40 years, as the number of cases increases four- to fivefold. As with all major illnesses, early detection and treatment will be critical factors in the successful management of AD. We would like to suggest that there are three major areas in which substantial progress needs to be made in order to successfully treat AD:

- Early detection and diagnosis
- Further development of symptomatic medications, and related treatment and care
- Development of disease-modifying medications

Early detection

We envision a time when routine screening for AD will be part of annual physical exams; perhaps the brief neuropsychological tests will even be performed at the community level, much like community screens for hypertension. The screens performed at the annual physical exam will likely be some combination of neuroimaging and brief neuropsychological tests; considerable progress has been made in both of these areas, as previously reviewed. In addition, there are numerous ongoing efforts to develop other techniques (e.g., electrophysiological or blood tests) to screen for AD. Hopefully, screening for AD will become as common as screening for hypertension, hypercholesterolemia and breast and prostate cancer. Of course, increased recognition and diagnosis will be most effective when paired with safe and efficacious treatments.

Symptomatic treatment

There are currently four symptomatic drugs approved for use as monotherapy, and one of these (memantine) is increasingly used as add-on therapy with one of the cholinesterase inhibitors. It seems likely that over the next 10 years, other symptomatic drugs will be approved. It is possible that the symptoms of the disease may eventually be treated with a cocktail of drugs; much like HIV is currently treated. As more is learned about the neurobiology and genetics of AD and other dementias, these cocktails may be tailored to different symptoms, different neurobiological markers and different genotypes. This approach, combined with effective and validated cognitive rehabilitation and care programs, may allow AD patients to function in the community for longer periods of time.

Disease-modifying treatments

Early detection and symptomatic treatment notwithstanding, all patients will eventually succumb to AD without a treatment that can substantially slow, and perhaps even eventually halt, the neurodegenerative process. Perhaps this is why the preponderance of drugs in clinical trials and in the pipeline are considered potential disease-modifying compounds. As we have reviewed, several of these compounds are now being evaluated or are about to be evaluated in Phase II and III clinical trials. While it is unlikely that any of the disease-modifying drugs currently in development will halt neurodegeneration, some may alter the slope of progression. Moreover, these drugs may also provide scientific and/or clinical insight that enables more effective disease-modifying compounds to be developed.

Looking back to 20 years ago, when a patient was diagnosed with AD intervention was limited to education and support; there were no drugs to treat the disease. The approval of tacrine (Cognex™) introduced the first treatment for AD [58]. Today, clinicians discussing the diagnosis of AD with patients and their families have multiple interventions to review. For example, there are combinations of approved

symptomatic medications that can be combined with disease-modifying medications that are in clinical trials. There are also sophisticated neuropsychological measures that can be combined with experimental neuroimaging techniques to help track patients' progress on their treatment regimen. Patients and families can be presented with behavioral and cognitive programs to help with mood, behavior and function. Concerned patients and families can also engage in conversations about genetic risk with their clinicians. To date, the efforts of many groups have already increased the awareness of the need for earlier diagnosis and access to interventions for AD; these efforts are evident in clinics where people are seen earlier in the disease [59]. We can only hope that the progress in the next 20 years will eclipse the progress of these past productive 20 years.

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Key issues

- There are currently an estimated 5.5 million cases of Alzheimer's disease (AD) in the USA. By the year 2040, there may be 16 million people with AD in the USA and 80 million worldwide.
- AD is underdiagnosed, and by some estimates only 50% of current cases are diagnosed and only 25% are treated.
- One of the keys to successful treatment of AD will be early diagnosis.
- Routine cognitive screening combined with emerging neuroimaging techniques to detect brain amyloid may help with early identification/diagnosis.
- Early treatment using emerging cognitive rehabilitation techniques holds promise for early treatment.
- Combining medications to treat symptoms has the potential to enhance cognition.
- Emerging disease-modifying medications have the potential to slow and perhaps ultimately halt the progression of AD.
- The combination of early detection/diagnosis following by a combination of symptomatic and disease-modifying medication seem to hold the greatest promise for successful management of AD.

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