Alzheimer’s Disease: Future Treatments

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Alzheimer’s disease has become a modern epidemic affecting more than 5 million persons in the United States and at least 30 million around the world. It accounts for nearly 60% of the causes of all persons with dementia. Death occurs within 10 years of diagnosis. A third to a half of persons with mild cognitive impairment go on to develop Alzheimer’s disease. Despite how common the condition is, the diagnosis is often not made by physicians and the diagnosis is first made in the long-term care facility. The disease begins with inability to remember newly learned items and progresses slowly to involve problems with language, executive function, and abstract reasoning. Early on, it can be associated with apathy and dysphoria. In the end stages, a variety of agitated behaviors may occur as well as true psychosis with illusions, delusions, hallucinations, and paranoia. When psychotic symptoms occur early, the diagnosis is more likely to be Lewy body dementia and, if there is marked apathy, fronto-temporal lobe dementia (Pick’s) disease should be a consideration. Vascular dementia is characterized by stepwise deterioration whenever the person has a small new stroke. Depression and other reversible causes of dementia should always be considered before other diagnoses are entertained. Figure 1 provides a simple approach to the diagnosis of dementia. Depression and delirium, including subsyndromal delirium, represent the most common reversible causes of cognitive impairment. At the end stage, Alzheimer’s disease can be associated with severe weight loss, seizures, problems with gait, and falls.

In view of the failure to recognize dementia by physicians, all newly admitted persons to a long-term care situation should be screened for dementia. Our preference is to use the Saint Louis University Mental Status Examination, as it should be screened for dementia. Our preference is to use all newly admitted persons to a long-term care situation for mild cognitive impairment (Figure 2).32,33 Although we recognize that a number of other appropriate screening tools exist.

Current treatments for Alzheimer’s disease have shown marginal clinical efficacy. Overwhelmingly, exercise appears to be safer and most probably more efficacious than any drugs approved for the treatment of Alzheimer’s disease or its associated behavioral problems. All nursing homes should provide daily (30-minute sessions) exercise for all residents. This should be the focus of recreation therapy in nursing homes. In addition, cognitive activities may also improve outcomes.

APPROVED DRUGS

Drugs currently approved for the treatment of Alzheimer’s disease target neurotransmitters that are altered in Alzheimer’s disease. At present, these target the cholinergic system (donepezil, rivastigmine, and memantine) or the glutamatergic system (memantine). Based on animal studies, numerous neurotransmitters modulate memory, including serotonin and catecholamines as well as neuropeptides, such as neuropeptide Y. Thus, it is not surprising that the available drugs turn out to have statistical significance in improving symptoms but are deemed to be of marginal clinical utility. Their neuroprotective ability is debated. In addition, these drugs are expensive and it has been suggested that they are no more efficacious than the much cheaper, old-fashioned nootropics (eg, piracetam and hydergine). In most cases, these drugs can be withdrawn safely in nursing home residents, greatly reducing the polypharmacy burden.

Antipsychotics are widely used to treat nonpsychotic, demented patients in nursing homes. Which antipsychotics are excellent therapy for persons with psychotic behaviors, ie, illusions, delusions, hallucinations, and paranoia? Their utility for treating agitation is questionable. In addition, these drugs increase mortality and have a variety of other side effects including increasing hip fracture.

Although somewhat tongue in cheek, this is the question that should be asked of every responsible party before an antipsychotic is administered. Finally, psychiatrists are now often using 2 or more different antipsychotics together in difficult residents. Although this is an admirable approach to phronesis, it lacks any scientific evidence.

Testosterone is an anabolic steroid with potential utility in treating frailty. In the SAMP8 mouse model of Alzheimer’s disease, testosterone levels are low and testosterone replacement improves memory and reduces amyloid precursor protein. Cross-sectional studies have suggested that low levels of testosterone are associated with cognitive impairment. A recent study found that low bioavailable testosterone in males with mild cognitive

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Impairment is associated with a rapid advancement to Alzheimer's disease within a year. Low testosterone is associated with small hippocampal volume. In normal hypogonadal males, testosterone has a small effect on improving memory. Minimal studies are available in older hypogonadal men with Alzheimer's disease.

Although lowering cholesterol with statins has been suggested to possibly improve memory in Alzheimer's disease, there is little evidence in support of this.

**ANTI-AMYLOID THERAPIES**

The pathological hallmarks of Alzheimer's disease are the amyloid-beta plaques and the neurofibrillary tangles associated with phosphorylated tau protein (Figure 3). The amyloid hypothesis suggests that amyloid produces the disease either secondarily owing to the formation of amyloid plaques produced by the aggregation of amyloid-beta peptides or secondarily to direct effects of amyloid-beta oligomers, which can directly cause memory problems, increase oxidative damage, and cause phosphorylation of tau. An interesting recent problem with this hypothesis has risen as we have shown that amyloid-beta peptide at physiological doses actually enhances memory. It is only when it is overproduced that it leads to Alzheimer's disease. Absence of amyloid-beta peptide also results in memory deficits.

There are 2 pathways by which the amyloid precursor protein (APP) is cleaved. The enzyme, alpha-secretase, cleaves APP to produce an extracellular soluble APP alpha protein that is then digested by gamma-secretase. The products of these reactions do not lead to amyloid plaques. Alternatively, beta-secretase (BACE1) releases a shorter soluble APP beta, which is then processed by gamma-secretases to produce amyloidogenic amyloid-beta (Mainly 1–40 and 1–42).

A number of pharmaceutical companies have developed drugs to target the beta and gamma secretases. The thiazolidinediones (rosiglitazone and pioglitazone), which have been used to treat diabetes, act as beta-secretase inhibitors. Nuclear peroxisome proliferation-activated receptor gamma suppresses the production of beta-secretase and in addition...
ubiquinates APP leading to its degradation. Unfortunately, the phase 3 trial with rosiglitazone showed no effect on function or cognition. Antibodies to beta-secretase have undergone preclinical studies. A large trial with the gamma-secretase modulator, semagacestat, was recently reported in the press to have failed. Compounds to increase the activity of alpha-secretase resulting in more non-amyloidogenic APP are in phase I trials.

Our studies have focused on using an antisense developed against the mRNA for APP. We have shown that small antisenses to APP mRNA block the formation of the APP protein and amyloid-beta. These antisenses improve acquisition and memory in mice, reduce oxidative damage, and increase the rate of clearance of amyloid-beta from the brain. They cross the blood brain barrier and can be given peripherally. Clinical trials are being planned.
Antibodies to amyloid-beta improve memory and increase acetylcholine when given centrally.\textsuperscript{96,97} When given peripherally, they increase the clearance of amyloid-beta peptide from the brain.\textsuperscript{98} Vaccination to produce amyloid-beta antibodies led to encephalitis in some patients\textsuperscript{99} and failed to improve cognition and survival.\textsuperscript{100} Passive immunotherapy trials are ongoing. These antibodies can cause transient cerebral edema.\textsuperscript{88}

Another approach to decreasing amyloid-beta plaques is to target the degrading enzymes of amyloid-beta, ie, neprilysin and insulin-degrading enzyme.\textsuperscript{101}

\section*{TARGETING TAU PROTEIN}

Valproic acid inhibits glycogen-synthase-kinase 3 leading to reduction in tau hyperphosphorylation and is a histone deacetylase inhibitor. A trial in Alzheimer’s disease showed no effects on function nor cognition, but a possible effect on behavior.\textsuperscript{102,103} Methylene blue (Rember) is a preventer of tau aggregation and has antioxidant effects. In patients, the 60-mg, but not 100-mg, dose improved cognition at 1 year.\textsuperscript{104} However, there were problems with the formulation and new formulation is being tested. High doses of nicotinamide reduce some forms of phosphorylated tau and inhibits polymerization of micro tubules.

\section*{MITOCHONDRIAL DYSFUNCTION}

Mitochondrial dysfunction produces synaptic damage and apoptosis and may play a central role in the neurodegeneration of Alzheimer’s disease. Antioxidants, especially alphalipoic acid, potently inhibit brain damage in Alzheimer’s mouse models and reverse memory deficits.\textsuperscript{105} A long-term uncontrolled trial of alpha-lipoic acid in humans produced promising results.\textsuperscript{106} Cross-sectional studies in humans link antioxidants with dementia; however, controlled trials with vitamin E have failed to find positive effects on memory or function.\textsuperscript{107}

Latrepirdine (Dimebon) is a potent enhancer of mitochondrial function because of its ability to block the mitochondrial permeability transition pore. Despite encouraging preliminary results, it, too, has failed.\textsuperscript{108}

\section*{OTHER TREATMENTS}

Administration of nerve growth factor in patients with Alzheimer’s disease improved cognition.\textsuperscript{109} It also causes severe pain and weight loss. Intranasal therapy is now being tried.

Animal and epidemiological studies in humans have suggested a strong possibility that docosahexaenoic acid would improve memory.\textsuperscript{110,111} Unfortunately, clinical trials have been disappointing, but most probably of too short a duration to allow definitive conclusions.\textsuperscript{112,113} Phosphodiesterase 2A inhibitors may improve blood flow and stabilize synaptic plasticity.\textsuperscript{114} Abnormalities in nitric oxide synthase are found in mice models of Alzheimer’s disease.\textsuperscript{115}

\section*{CONCLUSION}

Although animal studies have been highly exciting concerning their potential to cure Alzheimer’s disease, the translation to humans has been disappointing. This may in part be because little attention has been paid to the essential role of amyloid-beta in learning and memory. It has been assumed that it is just a toxic agent. Now it appears that like thyroid hormone, it produces diseases if there is too little or too much.
Acetylcholinesterase Inhibitors
- Donepezil
- Rivastigmine (available as tablets and patch)
- Galantamine

NMRA Receptor Antagonists
- Memantine

Preventing Production of Amyloid-beta production
- Antisenses to amyloid precursor protein
- Anti-beta-secretase antibodies
- Modulating gamma-secretase production
- Immunization

Increasing Amyloid-beta Protein Clearance
- Passive anti-amyloid beta antibodies

Preventing Amyloid-beta Protein Aggregation
- Decreasing Tau Aggregation
- Increasing Amyloid-beta Protein Clearance

Other Treatments
- Testosterone in males
- Nerve growth factor
- Phosphodiesterase 9A inhibitors
- Docosahexanoic acid
- Other nutrients

Table 1. Therapies That Are Being Developed for Alzheimer’s Disease

<table>
<thead>
<tr>
<th>Therapy Type</th>
<th>Example Drugs</th>
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<tbody>
<tr>
<td>Acetylcholinesterase Inhibitors</td>
<td>Donepezil, Rivastigmine, Galantamine</td>
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much. In addition, like diabetes mellitus there clearly is more than one type of Alzheimer’s disease with multiple possible causes. Eventual successful treatments will need to take these points into consideration.

The therapies available for Alzheimer’s disease and those being developed are listed in Table 1. As drugs are developed to treat Alzheimer’s disease, it is essential that they are tested in Alzheimer’s populations living in nursing homes, so we can be aware of their true utility and toxicity.116

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