Whatever Happened to New Treatments for Alzheimer's Disease?

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In the United States, until the 1980s, only ergoloid mesylates (dihydroergotoxine mesylate) were approved for "senile mental decline," and no agents were approved for Alzheimer's disease. Subsequently, improved diagnostic criteria for Alzheimer's disease[1] and specific FDA approval criteria requiring both cognitive and global clinical improvement led to systematic trials. Four cholinesterase inhibitors and memantine were eventually approved to treat Alzheimer's disease, but their effects were limited to a small advantage over placebo that did not alter the long-term trajectory of cognitive decline. Around the turn of the century, the pathophysiology of Alzheimer's disease seemed relatively well understood, several new agents were starting development, and more effective treatments for Alzheimer's disease appeared within reach. Yet, in the past decade, no new treatment has been approved for use in Alzheimer's disease. In this article, the approved agents will be reviewed briefly, and the outcome of research with new agents will be discussed.

Neurotransmitter Approaches

Cholinesterase inhibitors. Activity of cerebral cortical choline acetyltransferase, the key enzyme in acetylcholine synthesis, is reduced in Alzheimer's disease along with the loss of cholinergic cell bodies in the nucleus basalis.[2,3] However, precursor loading and muscarinic cholinergic agonists proved ineffective.[4] In contrast, several inhibitors of acetylcholinesterase (AChE) did show a significant, though small, advantage over placebo, averaging 1–4 points on the 70-point cognitive subscale of the Alzheimer's Disease Assessment Scale.[5–7] Tacrine was the first such FDA-approved medication, but liver toxicity limited its use.

Donepezil is an FDA-approved long-acting piperidine-based highly selective and reversible AChE inhibitor. In long-term studies, when donepezil treatment is stopped, cognitive ability rapidly drops to the trajectory line extrapolated from patients receiving placebo.[8,9] The standard formulation of donepezil is 5–10 mg/d to treat mild to moderate Alzheimer's disease; 10 mg may be slightly more effective than 5 mg.[10] Donepezil is also available as an orally disintegrating tablet. A higher dose of 23 mg/d is available for moderate to severe Alzheimer's disease; it showed a small cognitive advantage over 10 mg, but with more adverse events.[11]

Rivastigmine, which has both AChE- and butyrylcholinesterase-inhibiting properties, is started at 1.5 mg twice a day taken with meals, increasing to 3 mg twice a day after 2 weeks and then to 4.5 mg twice a day and 6 mg twice a day based on tolerability. A transdermal formulation (4.6, 9.5, 13.3 mg/d) reduces gastrointestinal intolerance.

Galantamine is a reversible, competitive inhibitor of AChE and shows allosteric modulation of nicotinic receptor sites and presynaptic nicotinic stimulation. Daily doses of 16 to 32 mg were superior to placebo in controlled trials,[5,6] and daily functioning showed improvement in 1 trial.[7] Daily galantamine dosage ranges from 8 mg to 32 mg in divided doses. An extended-release once-daily formulation is started at 8 mg/d, increased to 16 mg/d after 4 weeks, and then increased to 24 mg/d after another 4 weeks if needed.

The different cholinesterase inhibitors have similar efficacy and similar side effects primarily related to cholinergic mechanisms. Nausea, vomiting, and diarrhea are the most common, ranging from 5% to 28% across studies,[5–7] with higher doses associated with more gastrointestinal side effects; some tolerance occurs over time. Muscle cramps, headache, dizziness, syncope, flushing, insomnia, weakness, drowsiness, fatigue, and agitation are less common.

Nicotinic agonists. Nicotinic acetylcholine receptors (nAChRs) are reduced in the temporal and frontal cortex in Alzheimer's disease. Nicotine can improve memory, cognition, and attention in Alzheimer's disease patients, but nicotine therapy is limited by peripheral and parasympathetic effects. Therefore, efforts have focused on selective CNS nicotinic agonists active at the α4β2 subtype of nAChRs that are common in the hippocampus.[12] There is pilot evidence for some cognitive benefit for nicotine without global improvement in patients with mild cognitive impairment (MCI),[13] and the α7 nAChR subtype continues to be investigated.

Glutamatergic therapies. Memantine is an uncompetitive *N*-methyl-D-aspartate (NMDA) antagonist that binds to the NMDA receptor-operated cation channels and may act by inhibiting calcium ion influx, thus modulating excitotoxicity. The FDA approved memantine for moderate to severe Alzheimer's disease in 2003. The combination of donepezil and memantine may be superior to donepezil alone,[14] but the benefit is less certain when memantine is added to ongoing donepezil treatment.[9] Memantine is initiated at 5 mg/d for 1 week and increased by 5 mg/d in divided doses to a maintenance dose of 10 mg twice per day. A new extended-release formulation is given once daily at 7, 14, 21, 28 mg daily using a similar titration schedule. Significant side effects are uncommon and can include dizziness, constipation, headache, and confusion. It has low potential for drug interactions.

Treatment Approach With Approved Compounds

Assessing response to the approved agents in Alzheimer's disease is often difficult because the medication effect is mainly stabilization or lack of worsening of cognitive function. Therefore, lack of rapid deterioration without significant adverse effects is typically sufficient justification to continue these medications.

Antiamyloid Therapies

Neuritic plaques, comprised largely of amyloid, and neurofibrillary tangles occur diffusely through the cerebral cortex and hippocampus in Alzheimer's disease. The "amyloid cascade" hypothesis posits that dysregulation in amyloid precursor protein (APP) leads to increased production of amyloid β protein ($A\beta_{1-42}$) and other Aβ peptide fragments. Downstream events include the development of extracellular amyloid plaques, neurofibrillar pathology (tangles), and cell death. Proteolytic cleavage of APP can occur via 3 different secretases, α, β, and γ. When α-secretase cleaves APP, generation of pathogenic Aβ species is precluded. If α-secretase activity is diminished or β-secretase activity is increased, the generation of pathogenic Aβ species is enhanced, a process also involving subsequent cleavage by γ-secretase.

Several antiamyloid therapeutic strategies have been tested. A small molecule γ-secretase inhibitor, semagacestat, failed to show efficacy, and function actually worsened.[15] γ-Secretase inhibition can block Notch signaling protein, thereby leading to adverse biological consequences. Off-target effects have limited the utility of γ-secretase inhibitors. Currently, γ-secretase modulators are being evaluated. Amyloid fibrils polymerize and aggregate into amyloid plaques, but antiaggregation agents have failed to show efficacy.[16,17] Active immunotherapy with AN1792 was toxic (18 of 300 patients [6%] developed aseptic meningoencephalitis), without cognitive advantage over placebo. Passive immunotherapy involves direct delivery of antibodies, but large-scale phase 3 trials with

solanezumab (LY2062430), a humanized version of the m266 monoclonal antibody that binds to the 16–23 amino acid region of $A\beta_{42}$, were negative, with a worsening of function at higher doses of drug.[18] A post hoc analysis of patients with mild severity combined across 2 studies showed an advantage for drug over placebo. Although bapineuzumab, another humanized monoclonal antibody, failed clinically in phase 3 trials,[19] there was initial evidence, not replicated subsequently, that its use was associated with reduction in brain amyloid load based on amyloid positron emission tomographic (PET) scanning with the use of Pittsburgh compound B.[20] These inconsistencies have led to differing viewpoints about the amyloid pathway as a valid therapeutic target in Alzheimer's disease. Bapineuzumab was also associated with brain microhemorrhages identified by magnetic resonance imaging, which may be related to the role of amyloid β protein in cell membranes and the vasculature.[21]

Biomarker and neuropathologic studies in patients with Alzheimer's disease, patients with MCI, and healthy subjects suggest that amyloid brain deposition is an early manifestation that precedes the clinical diagnosis by decades. If so, antiamyloid therapies may need to be instituted very early. Large-scale prevention trials in normal subjects positive for brain amyloid on PET scanning and trials in preclinical subjects at high genetic risk are underway. If these trials lead to positive results, the antiamyloid strategy will gain momentum as a prevention strategy for Alzheimer's disease.

Tau Therapies

Tau protein is the key component of neurofibrillary tangles; tangle burden, not plaque, correlates with dementia severity prior to death. Tau pathology occurs in several neurodegenerative disorders, and aberrant kinase phosphorylation of tau is associated with synaptic dysfunction, impaired cellular signaling, vulnerability to stressors, and Aβ accumulation. Glycogen synthase kinase 3 (GSK-3) inhibitors like valproic acid play an important role in signaling downstream effects including tau phosphorylation, but valproate failed to show neuroprotection in Alzheimer's disease in a large trial.[22] Lithium also inhibits GSK-3, but results from placebo-controlled trials have not been positive. Other antitau therapies are now entering the drug development phase.

Other Treatment Strategies

Intracranial injection of nerve growth factor was abandoned due to toxicity and lack of efficacy. Basic neuroscience and epidemiologic evidence suggested potential therapeutic potential for estrogen, but the Women's Health Initiative study observed increased rather than decreased risk of dementia with estrogen use.[23] After initial promise, controlled trials of statins,[24] omega-3 fatty acids using DHA,[25] histamine-3 receptor antagonists,[26] the monoamine oxidase B inhibitor selegiline,[27,28] *Ginkgo biloba*,[29] oral anti-inflammatory agents,[30] and human intravenous immunoglobulin have been negative. Vitamin E in high doses of 2,000 IU/d has had both positive[27,31] and negative[32] results, and vitamin D may be a potential treatment for patients with MCI and Alzheimer's disease who have low vitamin D levels.[33] Curcumin is also being studied.[34]

Modifiable Risk Factors for Neurodegeneration

Epidemiologic evidence suggests that the times of onset of cognitive impairment and dementia are influenced by interacting factors such as aging, genetic susceptibility or resistance, environmental factors including toxin exposure, head injury, smoking, and endogenous susceptibility or protective factors such as menopause, diet and obesity, exercise, degree of educational attainment, depression, chronic psychological stress, and social connectedness. Addressing these common modifiable risk factors for neurodegeneration may markedly lower the risk of dementia, and Alzheimer's disease, in the population.[35] However, the epidemiologic evidence has not been supported consistently in clinical trials in Alzheimer's disease, in which diet and exercise typically have minimal to no effects.[36] The association of diabetes with dementia, and the increase in insulin resistance in Alzheimer's disease,[37] has led to a trial with insulin nasal spray in MCI and Alzheimer's disease.

Symptomatic Versus Disease-Modifying Treatments

Symptomatic treatment of Alzheimer's disease focuses on improving cognition. Another approach aims to modify the disease, that is, slow progression. A third strategy is primary prevention, delaying the time to onset of illness. Delaying the onset of Alzheimer's disease by 5 years would halve its incidence given the average human lifespan.[38] Other avenues include preventing the disruption of synaptic physiology.[39] As knowledge evolves, future strategies are likely to significantly improve our therapeutic armamentarium in the fight against this devastating disease.

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Potential conflicts of interest: Dr Devanand has been a consultant for and received honoraria from AbbVie and Lundbeck.
Funding/support: Supported in part by National Institute on Aging grants R01 AG17761, R01AG041795, and R01AG040093.
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J Clin Psychiatry 2014;75(7):775–776 (doi:10.4088/JCP.14ac09246)

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