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Update on Treatments for Cognitive Decline in Alzheimer's Disease

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A B S T R A C T

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and a leading cause of dementia in the elderly. AD initially presents as mild cognitive impairment (MCI); later, as AD progresses, memory and cognition are destroyed, preventing the ability to carry out activities of daily living. The primary care provider may be the first to suspect MCI, and screening tests can help with diagnosis. Development of drugs for cognitive decline in AD has been slow; however new therapies are in the pipeline and discovery of biomarkers make early diagnosis and future treatment of AD hopeful.

Introduction: Pathophysiology of Alzheimer's Disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the leading cause of dementia in the elderly.[1] In years past, AD was diagnosed by brain biopsies showing beta-amyloid plaques and neurofibrillary, or tau, tangles considered the main diagnostic feature of the disease.[2] Beta-amyloid plaques are protein deposits that damage the spaces between nerve cells in the brain, interfering with nerve transmission and significantly affect memory. Tau (neurofibrillary) tangles are twisted protein fibers that build up within the nerve cell or neuron that destroy the ability of the neuron to transmit.[2,3] These beta-amyloid plaques and tau tangles in the brain cause the death of neurons, resulting in cognitive decline (CD) and result in the dementia of AD.[4]

It is now known that beta-amyloid plagues can be present in the brain of the patient with AD up to 20 years before diagnosis, making the earliest diagnosis of AD imperative for researchers and for the development of new treatment modalities.[5]

Currently, researchers are investigating biomarkers that can be identified in cerebrospinal fluid (CSF) by positron emission tomography (PET) to diagnose AD in its earliest stages before irreversible dementia sets in.[6] As AD progresses, it will impair memory, the ability to think clearly, and, eventually, inhibit the ability to perform simple activities of daily living. Symptoms appear more commonly after age 60; however, earlier onset of symptoms can occur. Pharmacological therapies are targeted at the pathophysiological basis of the disease and include current treatments such as acetylcholinesterase inhibitors (AChEI) and N-methyl d-aspartate (NMDA) receptor antagonist, which treat the late effects of AD and slow disease progression but do not provide a cure.[1]

Cost of AD

Currently, Medicare and Medicaid cover only 70% of the costs of care for the patient with AD, increasing the financial burden for individuals and families.[7] In 2019, the treatment of patients with AD will cost the United States $290 billion; almost $200 billion will be in Medicare and Medicaid payments. By 2050, the estimate is that AD will cost the nation more than $1.1 trillion dollars.[3] Patients with AD and other dementias have more hospital admissions; more chronic conditions such as heart disease, diabetes mellitus (DM), and kidney disease; more skilled nursing home care; home health visits; and adult day services than others their age, adding to these costs.[3]

Cognitive Decline in Alzheimer's Disease

CD in AD develops in stages, often beginning with mild cognitive impairment (MCI) where the instrumental activities of daily living are mostly intact.[8] MCI can be the first sign of AD; however, it is important to consider that it can be a sign of systemic, psychiatric, or other neurologic conditions.[8]

Mild Cognitive Impairment

MCI is a stage between the normal CD of aging and dementia; patients with memory and executive function deterioration have a high risk of progressing to dementia.[9] American Association of Neurology (AAN) states the progression to dementia in those older than 65 years with MCI is 14.9%, and the risk of MCI increases with age.[9] Patients with MCI may progress to dementia, remain stable, or return to a neurologically intact status.[9]

There are no evidence-based studies indicating that pharmacologic therapies for MCI are effective.[9,10] Definitions of MCI and AD can be confusing, a new definition for AD proposes that the diagnosis be confined to the presence of biomarkers for amyloid and tau,[11] but if only amyloid pathology is present, the label would be changed to "AD Pathologic Change"; both diagnoses are independent of the clinical status of the patient.[9] Other definitions exist for MCI, such as "cognitively impaired, no dementia."[9] In patients with

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mild cognitive impairment, the AAN recommends regular exercise and no drugs or supplements.[9] However, patients with MCI commonly have behavioral and neuropsychiatric symptoms and should be offered nonpharmacologic treatments that include eliminating physical and emotional stressors, modifying the environment, and establishing daily routines. If needed, it may be necessary to prescribe off-label antipsychotics using the smallest effective dose for the shortest possible duration to minimize adverse effects.[12]

Diagnosis of AD Dementia

AD dementia has three general stages (mild, moderate, and severe) with the moderate stage being the longest. AD dementia (ADD) may begin as MCI and will progress through stages affecting all activities of daily living; as dementia progresses, the person will have memory loss, lose ability to carry out executive functions, have trouble communicating, and, in the final stage, will lose bodily functions, become bedbound and ultimately die from the disease.[13] Diagnosis is often a combination of family and patient interviews, cognitive, psychological, and neurological examinations, and clinical evaluation.[14]

Cognitive Screening

The AAN recommends screening for MCI during the annual Medicare Wellness Visit; if positive, further in-depth testing should be undertaken.[8,9] AAN Guidelines recommend screening for MCI with validated tools; its position is that no instrument is superior to another, and the diagnosis of MCI should be based on a clinical evaluation to determine between MCI and dementia.[9] Pinto and colleagues[15] determined in their study that the Montreal Cognitive Assessment is better at detecting MCI; however, they found that both MoCA and the Mini-Mental State Examination are valuable in detecting AD. Conditions that exacerbate or cause CD, including hypothyroidism, vitamin D deficiency, anemias, hypercalcemia, folate deficiency, and infection should be evaluated and, if suspected, ruled out by laboratory testing and thorough physical evaluation.[16]

When evaluating patients over age 65 for symptoms of CD, a medication review is imperative. The updated Beers criteria from the American Geriatric Society Expert Panel list the following medications with highly anticholinergic effects in the elderly and the risk of contributing to CD. First and second (atypical) generation antipsychotics are to be avoided except in bipolar disorder or schizophrenia or short-term use as a chemotherapy antiemetic. All benzodiazepines increase the risk of cognitive impairment and delirium in older adults (see Box).[17]

Assessment of cognitive function should begin with a history of cognitive changes over time, confirmed by a family member or significant other, if possible. The provider should document the onset, and types of cognitive occurrences over time to obtain a thorough history. It is helpful if a family member or caregiver keeps a diary of symptoms. Neuropsychological testing should evaluate all cognitive domains, including executive function, attention, visuospatial skills, memory, and language.

Validated screening tests useful for detecting MCI include the Mini-Cog, Addenbrooke's Cognitive Examination, the Cambridge Cognition Examination, the MoCA, Consortium to Establish a Registry for Alzheimer's Disease,[18] and the Saint Louis University Mental Status (SLUMS) examination.[19]

Current Treatment for Cognitive Decline in Alzheimer's Disease

The CD of AD is caused by the loss of cholinergic neurons resulting in decreased neurotransmission in the synaptic clefts of the brain.

Box
Medications With Anticholinergic Properties

First-generation antihistamines:

- Hydroxyzine
- Meclizine
- Promethazine
- Diphenhydramine (oral)

Antispasmodics

- Atropine (excluding ophthalmic)
- Scopolamine

Antidepressants with strong anticholinergic properties

- Amitriptyline
- Desipramine
- Imipramine
- Nortriptyline

Source: American Geriatrics Society Beers Criteria Update Expert Panel et al., 2019).[17]

AChEI are centrally acting medications FDA approved to treat cognitive symptoms by delaying the breakdown of acetylcholine (ACh), resulting in increased ACh in the brain. The following medications are FDA approved for the treatment of AD: donepezil, rivastigmine, galantamine, memantine/donepezil,[20] and memantine.

The key of treatment is always start low and increase the dose slowly to reduce side effects; which may include nausea, vomiting, anorexia, and diarrhea to avoid patients stopping treatment. Donepezil and rivastigmine are approved for severe AD dementia. Memantine, an NMDA glutamate receptor antagonist, reduces glutamatergic neuronal excitotoxicity and is approved for moderate to severe AD dementia either as monotherapy or in combination with AChEI (Figure).[21]

Antipsychotic Use in AD Dementia

Tampi and colleagues reviewed the literature indicating the use of risperidone, olanzapine and aripiprazole for the treatment of aggression and psychosis in patients with AD to have mild benefits.[22] The U.S. Food and Drug Administration (FDA)[23] has issued warnings the these medications need to be reserved for severe psychosis and agitation unresponsive to nonpharmacological strategies because of their severe potential side effects, including CD, cardiovascular events, and death[22,24]

Advances in Biomarkers

Currently, there are no biomarkers available that clearly predict progression of MCI to dementia. The most common biomarkers used in clinical trials are CSF amyloid, volumetric magnetic resonance imaging, amyloid PET scan, and CSF tau[25] A novel biomarker being used to determine injury to neurons is the plasma neurofilament light, which can be useful in gaging CD.[26] The Early Identification of AD and Related Dementias Biomarkers Study discovered beta amyloid and tau changes in neuroimaging years before the first symptoms of AD appear[27] that will potentially enable clinicians to diagnose and treat AD years before ADD occurs. Biomarkers are increasingly important in the study of AD therapies as well as for future treatment and diagnosis of AD. Biomarker research is a rapidly evolving field, and patients who are interested may be referred to sources that can connect patients to this research.[28]

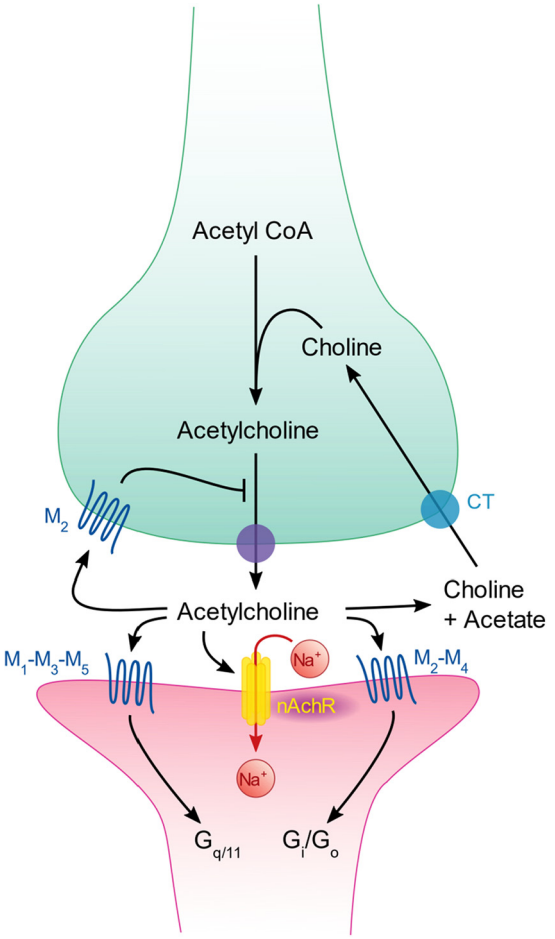

Figure. Image outlines major routes of transport of acetylcholine (ACh) within a cholinergic synapse in the brain (shown). Current drug therapies propose AD is caused by reduced synthesis of the neurotransmitter ACh. Acetylcholinesterase inhibitor medications (AChEI) are used to reduce the rate of ACh break down to reverse the loss of ACh caused by the death of cholinergic neurons in AD (not shown).[49] Figure created by Smedlib, based on original work by Pancrat - Own work, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=60354630.

Pharmacologic Clinical Trials to Prevent CD

Phase 1 clinical trials involve a small number of volunteers who participate for a few months to see if a drug or product is safe. About 70% of drugs in Phase 1 proceed to Phase 2 trials, which involve up to hundreds and may take up to 2 years to test the efficacy and side effects of the drug or product. Approximately 30% will move on to Phase 3. In Phase 3, there can be hundreds to thousands of volunteers, and studies may last from 1 to 4 years.[29]

Cummings and colleagues[23] reviewed Clinicaltrials.gov in February 2019 to determine therapies in the AD pipeline and noted a total of 132 agents in clinical trials; 19 agents for cognitive enhancement, 96 for disease modification, 14 for neuropsychiatric or behavioral symptoms, and 20 monoclonal antibodies or biological therapies. Amyloid continues to be the primary target in disease modifying trials. Only drugs being investigated for cognitive enhancement are discussed here.

Disease-Modifying Therapies (DMT) Small Molecule

Investigative therapies for enhancing cognition include the anticonvulsant medication *levetiracetam*, which is hoped to reduce neuronal hyperactivity and is currently in trials scheduled for completion in 2022.[23]

Intranasal detemir insulin and liraglutide (glucagon-like peptide I receptor agonist) were hoped to increase cell signaling and growth and were being evaluated for effects on amyloid plaque formation and tau deposits in the brain; placebo controlled trials showed no effect in mild to moderate AD.[23]

Humulin insulin intranasal (aspart, glulisine) is being studied to replace insulin in the brain, to enhance cell signaling and neurogenesis. *Rasagiline* (monoamine oxidase B inhibitor) is being evaluated for enhancing mitochondrial activity and inactivate reactive oxygen species.[23]

RAGE is the receptor for advanced glycation end products; a member of the immunoglobulin family, it contributes to cognitive impairment through beta-amyloid production and formation of neurofibrillary tangles.[30] *Azeliragon* is an oral RAGE inhibitor being evaluated to decrease CD by binding to RAGE and preventing it from binding to other proteins that cause the inflammatory process that leads to AD. In 2018, randomized controlled trials (RCTs) were discontinued due to lack of efficacy. In 2019, a posttrial review showed cognitive improvement, a decrease in dementia, and a reduction in inflammation in mild AD patients with diabetes type 2. A new trial was initiated in 2019 to investigate the safety and efficacy of azeliragon in patients with mild AD and diabetes.[31]

DMT Biologics

Solanezumab is a monoclonal antibody infusion that promotes beta-amyloid clearance in the brain; it was not effective in delaying CD in Phase 3 clinical trials in patients with mild AD[32] and was not approved by the FDA.[33]

Clinical trials for immunotherapy agents (*gantanerumab, aducanumab, BAN2401*) produced plaque removal and were hoped to delay CD in patients with early AD. None of the agents were found to be efficacious except aducanumab in a small trial that slowed CD at a high dose.[34] Clinical trials to assess gantenerumab and solanezumab in patients with dominantly inherited AD (a rare, early-onset type) will finish in December 2023. Gantenerumab in higher doses is currently being trialed for prodromal to mild AD.[35]

Beta-Secretase Enzyme (BACE) Inhibitors

Verubecestat, lanabecestat, and *elenbecestat* are BACE inhibitors hoped to prevent beta-amyloid plaque production in the brain, CSF, and blood. BACE is a beta-secretase enzyme that cleaves the amyloid precursor protein, the initial step for production of beta-amyloid molecules in the brain. Most of these investigational drugs failed in RCTs for mild-to-moderate AD[36] and were discontinued due to side effects.[37] Studies are being continued to evaluate efficacy in patients in early stage AD.[36]

Symptom-Reducing

Idalopirdine is a selective 5-hydroxytryptamine-6 receptor antagonist tablet evaluated for the treatment of cognition in mild to moderate AD; study findings were not efficacious.[38] Other repurposed drugs targeted for cognitive enhancement include *montelukast buccal* film (to reduce inflammation in mild-moderate AD) for which a trial will end in 2020 and a *transdermal nicotine* (to enhance acetylcholine signaling) trial, which will end in 2019.[23]

Nutritional Supplement

Souvenaid, a combination of phospholipids; folic acid; uridine monophosphate; eicosapentaenoic acid; docosahexaenoic acid;

choline; vitamins C, E, B_{12}, and B_6; and selenium, is a nutritional supplement hoped to support neuronal function as evidence shows these nutrients may be reduced in patients with AD.[39] Early clinical trials showed that Souvenaid increased the availability of these nutrients and may improve memory performance.[32] A later clinical trial of Souvenaid infusion in AD patients with MCI found no effect on cognition.[33]

Over-the-Counter Treatment

There are a multitude of over-the-counter (OTC) therapies currently on the market or under investigation for the treatment of CD in AD. *Vitamin E (alpha tocopherol)* was thought to exert a protective effect through antioxidant qualities on cortical neurons in patients with dementia. Several small studies suggested benefit in patients with mild to moderate ADD receiving 2,000 IU daily.[40] However, RCTs indicated no evidence that vitamin E prevented progression to dementia or that it improved cognitive function in patients with MCI or ADD.[41] Butler and colleagues[42] performed a systemic review of 38 trials of OTC supplements including *alpha-3 fatty acids, soy supplements, vitamin B, calcium plus vitamin D, ginkgo biloba, beta-carotene,* and *vitamin C* and found no benefit in MCI or in ADD patients. Their results indicate these OTC supplements should not be recommended to improve MCI or ADD.[42]

Devices for Treatment of AD and Cognitive Enhancement

Devices that target brain stimulation for the purpose of enhancing cognition or clearing tau or amyloid deposits through stimulation are under investigation. Some of these devices include deep brain stimulation with implanted electrodes, electroconvulsive therapy, transcranial pulse stimulation, laser therapy, and surface application of electric current.[28]

Nano-Based Drug Delivery

Currently medications to treat neurological diseases like AD have to overcome the blood-brain-barrier (BBB). A new technology using nano-particles to encapsulate drugs can cross the BBB and provide targeted and longer acting therapy. Nano-particles can consist of organic, inorganic, polymeric and metallic nanostructures that can be used as targeted and controlled drug delivery vehicles.[43]

A vaccine for AD *(AADvac1)* that produces an immune response against the tau protein that causes neurofibrillary tangles is being tested in clinical trials; in 2017, it was announced AADvac1 had a good safety profile, and in 2019, 98% of patients given the vaccine developed antibodies to the tau protein. Clinical trials are ongoing to determine the effect on cognition.[44]

Conclusion

AD is a complex and debilitating neurological disease that has been researched for decades, but few new drugs have been approved for treatment of AD or CD. Recently, the theories of AD pathophysiology such as the cholinergic, amyloid, and tau theory of pathology used for treatment modalities are being reconsidered due to the high failure rate of many drugs in the disease modifying, symptom reducing, or cognitive enhancing therapy targets.[45] Pharmacological therapies in the pipeline as of 2019 include DMTs, symptom-reducing therapies, and symptomatic agents for cognitive, neuropsychiatric, and behavioral changes. Research and clinical trials are ongoing for nutritional and OTC supplements to increase cognition, but results have been disappointing to date.[32,46–48] Trials of repurposing existing drugs such as insulin, antiseizure medications, and others to determine their effect on enhancing cognition have also been disappointing.[23]

Promising new research has primarily been in the areas of nonpharmacological therapies for patients and caregivers such as lifestyle changes, exercise, good nutrition and social activity, new biomarkers, new imaging modalities, and novel devices to reduce the symptoms of AD.[6,26,32,48] Research using nano-particles to deliver drugs more efficiently to the brain for treatment of ADD is promising.[43] AAN recommends that patients and families diagnosed with MCI be counseled to discuss advance directives, finance and estate planning, and driving safety.[8]

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