Update on Treatment Options for Dementia

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Alzheimer’s Disease (AD) is a common neurodegenerative disorder characterized by progressive memory loss and cognitive decline. Neuropathologically, AD is characterized by the presence of extracellular accumulation of amyloid β peptides (Aβ) and intracellular neurofibrillary tangles of hyperphosphorylated tau protein. Amyloid plaque accumulation starts many years before the onset of the cognitive decline, indeed at the time the patient has clinical signs of dementia the accumulation of amyloid reaches a plateau. The symptoms of dementia appear to correlate mainly with the accumulation of intracellular neurofibrillary tangles. Although there is no treatment to correct the pathological process that leads to AD, there is a large window of opportunity to treat this condition before it becomes clinically evident.

PREVENTIVE TREATMENT OF AD

Detection of the disease before it is clinically evident is challenging, however there are several ways to identify individuals at risk. Besides age, which is the most important risk factor, the presence of APOE ε4 allele accounts for 20-50 percent of the attributable risk. Obviously, there are no current strategies to treat these two factors. Nonetheless, there are modifiable risk factors that have been associated with AD, including vascular disease, anemia, diabetes, depression, living alone, and low education level. These factors have been quantified as frailty index, and improvement of the general health with special attention to these factors may decrease the risk of developing AD. In addition, persons who engage in stimulating activities at least twice a week (attending organizations, practicing an artistic activity, playing cards or crossword puzzles) may further decrease the risk.

Dietary treatments. Vitamin A, present mainly in carrots, broccoli, pumpkin, dairy products, liver, and eggs, possesses antiapoptotic, antioxidant, antiamyloidogenic, and anti-inflammatory activities. In AD mouse models, administration of all-transretinoic acid (ATRA) decreases amyloid accumulation and tau hyperphosphorylation and improves cognitive decline. Phase II studies are ongoing to test the effect of retinoid supplementation in AD.

Complex B Vitamins, present in meats, legumes, whole grains, potatoes, bananas, chili peppers, etc., are essential for brain function. Deficiency of these vitamins has been associated with dementia and increase of the amyloid burden in animal brain. Supplementation in individuals with normal vitamin B12 levels has not shown evidence of preventing or improving dementia symptoms. Measurement of Vitamin B12 and folate and supplementation when levels are low is recommended to avoid deficient states.

Vitamin C, present in citrus fruits, strawberries, kiwis, and green leaf vegetables, such as spinach and broccoli, has been suggested as a potential preventive treatment for its antioxidant effect. A mouse model study examined the potential benefit of vitamin C, showing that high doses of ascorbic acid decrease amyloid plaques burden in the cortex and hippocampal brain of mice. Currently there are no clinical studies that demonstrate the preventive or therapeutic effect of vitamin C in AD.

Vitamin D is synthesized in the skin following sun exposure and is present in fish and eggs in noteworthy concen-
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Vitamin D has important roles in calcium signaling within the brain, and neurotrophic and neuroprotective actions. Vitamin D deficiency has been associated with increased risk of all cause dementia including AD, and supplementation is recommended in individuals with low levels.

Vitamin E is a lipid-soluble compound and is present in the majority of vegetable oils in all four tocopherol forms. It is present in wheat germ, oats, hazelnuts, corn, sunflower seeds and palm oil, rice bran oil, and poppy seed oil in the tocotrienol form. Vitamin E prevents the activation of p38MAPK, which is essential for the phosphorylation of neuronal tau molecules. Diet supplementation of vitamin E to double transgenic mice of AD prevented increase of p38 in the cortex of these animals. Clinical studies have not demonstrated a preventive or therapeutic effect in patients with AD or MCI.

Vitamin K is also a lipid-soluble compound and is present in leaf vegetables, certain vegetable oils, fruits, tubers, and seeds. The role in the pathogenesis of AD is unclear, but in a cohort of patients with early AD the dietary intake of vitamin K was significantly less compared to a control group, and patients who took vitamin K antagonists were more likely to have cognitive impairment. There is no clinical evidence that vitamin K supplementation may prevent or improve AD.

Caffeine is a psychoactive stimulant resulting in heightened alertness, arousal and improvement of cognitive performance. The effect of long-term caffeine effect in the brain is not known; some case-control and cross-sectional and longitudinal population-based studies provided some evidence that caffeine consumption or higher plasma caffeine levels may be protective against cognitive impairment and dementia.

Ethanol (Alcohol) protects neurons against Aβ-induced synapse damage induced by A-synuclein and has been suggested as a preventive treatment. Longitudinal population based studies demonstrated lower risk in light-to-moderate drinkers, whereas there is an increase of the dementia risk in heavy drinkers.

Mediterranean diet consists of fruits and vegetables, low in red meats, high in olive oil and moderate red wine. In part, the effect of the diet has been attributed to oleo-canthal, a phenolic component of extra-virgin olive oil. Oleocanthal effect in vivo and in vitro improve the brain clearance of beta amyloid. Meta-analysis of clinical studies with longitudinal follow up to at least one year reported that adherence to Mediterranean diet was associated with lower risk of MCI and AD.

In summary, diet appears to be a critical modifiable factor to prevent AD. Vitamin deficiencies are a potential risk factor for AD, and vitamin levels, particularly folate and B₁₂, should be performed even before clinical symptoms of AD in susceptible individuals. Vitamin supplementation without a clear deficit does not appear to be effective, and there is a risk of potential toxicity.

PHARMACOLOGICAL THERAPY

Cholinesterase inhibitors. Patients with AD have a progressive decrease in levels of neurotransmitters, particularly ACh. Development of cholinesterase inhibitors was a rational step to increase the levels of ACh in patients with AD hoping for clinical improvement of the cognitive deficits.

Tacrine was the first approved drug of this class but is rarely used today. It has been tested for efficacy in the management of AD in six studies involving more than 2,000 patients, demonstrating less decline on cognitive testing compared with placebo-treated patients. The most troublesome adverse effect was hepatotoxicity with elevation of transaminase levels nearly in half of subjects. In addition, Tacrine requires four times daily administration which is a problem for compliance.

Donepezil is a centrally acting reversible acetylcholinesterase inhibitor with a long elimination half-life of 70 hours and is administered once daily. Donepezil is metabolized by cytochrome P450 (CYP) 2D6 and CYP3A4 in the liver. In three double-blind, placebo-controlled trials lasting from 12 to 24 months, donepezil produced a significant drug–placebo difference on neuropsychological test and clinician’s assessment. Gastrointestinal side effects account for the majority of adverse effects in up to 17 percent of subjects. Lower dose of 5mg was better tolerated than 10mg daily, and there was no clear difference between the efficacy between these doses.

A larger dose of 23mg was approved based on a randomized, double-blind study showing better cognitive function in the 23mg dose group. However there was much higher drop out rate and higher GI side effects in the 23mg dose arm. There is no evidence to support the use of donepezil for patients with MCI. The possible benefits are minor and short lived without evidence that donepezil delays the onset of AD. In addition, donepezil use is associated with significant side effects.
Rivastigmine is a so-called ‘pseudo-irreversible’ inhibitor of two enzymes, acetylcholinesterase and butryrylcholinesterase. It is well suited to transdermal delivery because it is a small lipophilic and hydrophilic molecule but it is also available in capsules. 28 The half life of the drug is very short (1–2 hours), but the duration of action is longer, as the enzymes are blocked for around 8.5 and 3.5 hours, respectively. 29 Efficacy and tolerability was assessed in a double-blind, double-dummy, placebo- and active-controlled study showing significant improvement relative to placebo. The transdermal patch had similar efficacy than the pill but it has significantly fewer GI side effects. 20 cm2 dose group obtained higher cognitive scores compared to 10 cm2 dose. 28

Galantamine is also a selective acetylcholinesterase inhibitor but also modulates presynaptic nicotinic receptors. It has a half-life of 6-8 hours and is mainly metabolized by cytochrome P450, CYP2D6, and CYP3A4 in the liver. 30 Meta-analysis of studies using galantamine in mild to moderate AD has shown significant improvement in cognitive testing during three and six months trials. Side effect profile is similar to other anticholinesterase drugs. Once-a-day extended release preparation has similar efficacy and tolerability as the standard twice-a-day dosing. The trial on MCI showed no significant benefit, and one unexplained death was reported. 30 A transdermal patch was recently developed but has not been tested yet in patients with AD. 31

In summary, anticholinesterase agents are the mainstay treatment for moderate dementia without clear effect on progression of the disease. It appears to produce a transient symptomatic relief of the low ACh levels associated with AD. There is no evidence of efficacy in MCI or mild dementia. Among the approved anticholinesterase drugs, there is no difference in efficacy. Transdermal delivery appears to improve the GI side effects. Higher doses appear to be more effective, at least in short term cognitive and behavioral measures, but it also cause more side effects and lower long term adherence to treatment.

NMDA receptor antagonist. Memantine was introduced for potential treatment of AD because of the anti-glutaminergic effect. Memantine mechanism of action as a low-to-moderate affinity, noncompetitive, N-methyl-d-aspartate (NMDA) receptor antagonist, prevents calcium entrance to the cell and decreases the neuronal dysfunction created by high levels of glutamate. 32 Memantine also works at dopamine D2 receptors, block alpha7 nicotinic ACh receptors, and antagonizes 5HT3 receptors. The effects on these receptors in AD is not known. 33–35 Memantine has a long half-life of 70 hours; it is excreted unchanged in the urine. 25 Memantine is well tolerated but lacks efficacy in MCI and mild dementia. 36 In patients with moderate to severe dementia there was a significant improvement but the study was limited by a significant dropout rate (28 percent). 37 When memantine was added to donepezil in patients with mild to moderate AD, there was no significant change. 38 Meta-analysis of randomized controlled studies slightly favored combination therapy in patients with moderate to severe AD but was not enough to recommend the combination therapy. 39 However, longitudinal studies have shown that combination therapy is associated with better cognitive outcomes and greater delays in time to nursing home admission versus mono-therapy or no treatment. 40

**Future drugs.** New lines of drugs are being developed aiming to reduce amyloid burden, targeting the pathological accumulation of beta amyloid. The association between amyloid deposits and cognitive dysfunction is not clear, in fact the accumulation of beta amyloid plateaus at the onset of the clinical symptoms. Of note, there is a small group of individuals with high amyloid burden and normal cognition.

MLC601 is a traditional Chinese medicine with possible modulatory effect of the amyloid precursor protein processing. A multicenter, non-blinded, randomized controlled trial showed good tolerability with no significant difference in efficacy compared to donepezil, rivastigmine and galantamine. 41 The effect on amyloid burden has not been established yet.

Passive and active amyloid-based immunotherapy has been effective to clear brain amyloid deposits. The vaccine AN1792 has shown to reduce the amyloid burden but did not improve cognitive function in patients with AD. Postmortem brain pathological examination of these patients showed that the vaccine accelerated the death of diseased neurons, which correlated with increase of brain atrophy after vaccination. Some patients developed meningoencephalitis after active immunization. 42 Passive immunization with bapineuzumab, a humanized monoclonal antibody directed towards the N-terminal of the beta amyloid, didn’t improve clinical symptoms but decreased fibrillar

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amylloid accumulation. Another monoclonal antibody, solanezumab, directed to the mid-region of the beta amyloid, failed to improve clinical symptoms of mild to moderate AD patients. More studies are still ongoing with second generation active vaccines (ACC-001, CAD106 and Affitope AD02) and new passive immunotherapies against amyloid and tau protein in patients with high risk asymptomatic or MCI individuals. It makes sense to target the main pathological protein accumulation in the brain. Current data support the efficacy to decrease the burden of amyloid and tau, but we have yet to see a clinical effect. Perhaps these therapies may prove effective in the pre-clinical stage to prevent the disease.

TREATMENT OF BEHAVIOR SYMPTOMS OF DEMENTIA

In patients with moderate to severe dementia, behavior disorders are quite common and account for significant disability and social issues. Depression is very common, and it may blur the diagnosis and grading of AD. SSRIs are proven advantage against NMDA receptor-mediated neurotoxicity. J. Neurosci. 12, 4427–4436 (1992).


