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Update on Cholinesterase Inhibitors and Treatment of Alzheimer's Disease

The long-term studies of the cholinesterase inhibitors, Aricept (donepezil), Razadyne (galantamine) and Exelon (rivastigmine), support their ability to delay Alzheimer's disease (AD) progression during the dementia stage by 1, 1.5, and 2.5 years respectively, which underscores the importance of early detection to optimize quality of life. Cholinesterase inhibitors reduce caregiving burden by delaying AD progression. A one-year randomized study showed that caregivers spent 12 hours per day taking care of AD patients receiving placebo, whereas those receiving Aricept required 10.1 hours of caregiving daily. This difference amounted to an extra 10 weeks of caregiving per year for untreated AD patients [1].

Tacrine was the first cholinesterase inhibitor approved to treat AD. A two year study comparing high doses (80 to 160 mg/day) to low doses (<80 mg/day) in mild to moderate AD patients showed that the patients on high doses were 1.75 times less likely to be placed into a nursing home after two years of treatment [2]. Time to death did not differ between the two groups.

Aricept (donepezil) – Aricept is a weak inhibitor of acetylcholinesterase, and is FDA-approved for mild, moderate and severe AD. After one year of treatment, cerebrospinal fluid levels of acetylcholinesterase increase well above baseline [3], which suggests a time-limited effect of Aricept. An open label study of Donepezil in 133 AD patients for approximately 3 years showed a significant reduction in the rate of cognitive decline as measured by the ADAS-Cog [4]. Other studies treating AD patients for up to five years show that after 3 years, the rate of decline approaches that of the natural history of AD. Overall, there appears to be an approximate 33% reduction in the rate of decline of AD for up to 3 years, which is equivalent to a delay of approximately 1 year.

Razadyne (galantamine) – Razadyne is FDA-approved for mild to moderate AD. In addition to weakly inhibiting acetylcholinesterase, Razadyne allosterically binds to the presynaptic nicotinic acetylcholine receptor, which increases presynaptic acetylcholine release, and increases release of many other neurotransmitters. In experimental animal models, Razadyne blocks programmed neuronal cell death (apoptosis), reduces levels of unbound beta amyloid to reduce glutamate mediated excitotoxicity, and reduces cholinergic neuronal cell death. Three year studies of Razadyne in AD patients have demonstrated an approximate 50% reduction in rate of cognitive decline using the ADAS-Cog [5]. Overall, there appears to be a 50% reduction in rate of decline in AD for at least three years, which is equivalent to a delay of 1.5 years or longer.

Exelon (rivastigmine) – Exelon is FDA-approved for mild to moderate AD. It is a strong inhibitor of acetyl- and butyryl-cholinesterase that does not develop tolerance for at least one year of treatment [3]. Butyrylcholinesterase inhibition may reduce neuritic plaque formation in AD patients [6]. In AD patients treated with Exelon for five years, their rate of decline was reduced by an average of 54% [7], which is similar to the reduction achieved by Exelon given to 532 mild to moderate AD patients over 2.5 years [8]. Overall, there appears to be a 54% reduction in rate of decline in AD for at least five years, which is equivalent to a delay of 2.5 years or longer.

References

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Proposed New Diagnostic Criteria for Alzheimer's Disease Emphasizes Early Detection

An international group of researchers led by Bruno Dubois, MD from Hôpital de la Salpetriere and the Université Pierre et Marie Curie in Paris, France has proposed new diagnostic criteria for Alzheimer's disease (AD). Current criteria for diagnosing AD is based on the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* published in 2000 and the Neurological Disorders and Stroke-Alzheimer's Disease and Related Disorders (NINDS-ADRDA) diagnostic guidelines published in 1984. According to these guidelines, physicians apply AD diagnostic guidelines once a patient exhibits dementia symptoms and thus make the diagnosis when the patient is demented.

The proposed diagnostic criteria recommend use of early memory testing to help to define the specific amnestic syndrome of the hippocampal type that is characteristic of AD. Furthermore, for a diagnosis of probable AD, patients should have at least 1 or more abnormal biomarkers among several supporting tests: structural neuroimaging on MRI looking for hippocampal atrophy; a specific metabolic pattern on molecular neuroimaging with PET and CSF analysis of amyloid-beta or tau proteins; or the presence of 1 of 3 autosomal dominant mutations related to AD on genetic testing.

Reference: Dubois B et al. Lancet Neurology. 2007; 6(8):734-46.

Retinopathy May Lead to Reduced Cognitive Function

Researchers at the University of Melbourne Centre for Eye Research, Australia studied the relationship between retinal microvascular manifestations and reduced cognitive function and dementia. The study included 2,211 subjects aged 69 to 97 years. Retinal photographs were taken at enrollment into a cardiovascular health study and were evaluated for retinopathy signs, such as microaneurysms and retinal hemorrhage and for symptoms, including focal arteriolar narrowing. More than half of the patients had hypertension. The Digit-Symbol Substitution Test was used to evaluate cognitive status. After adjusting for factors such as age, hypertension, diabetes, and cigarette smoking status, subjects with retinopathy had lower cognitive status than those without. In subjects with hypertension, retinopathy carried an adjusted odds ratio of 2.10 for dementia. For focal arteriolar narrowing, the corresponding odds ratio was 3.02.

Reference: Baker ML et al. Stroke. 2007; 38(7): 2041-7.

Elevated Beta-Amyloid Levels in Down's Syndrome Patients Associated with Earlier Onset of Alzheimer's Disease

It is often assumed that because all adults with Down's syndrome (DS) have elevated levels of beta-amyloid, they will develop Alzheimer's disease (AD). A recent study led by Dr. Schupf of the Taub Institute for Research on Alzheimer's Disease and the Aging Brain, New York found that subjects with higher levels of beta-amyloid were more likely to develop AD. The study included 204 subjects with DS who were 45 years or older. At baseline, 30 had AD. During a mean of 3.9 years of follow-up, 44 participants developed AD. Those with medium and high levels of beta-amyloid were twice as likely to develop AD when compared to those with lower levels. Subjects with the highest levels of beta-amyloid were also more than twice as likely to die during the study period when compared to those with the lowest levels of beta-amyloid. There was no difference between the mortality rates of subjects with medium and low levels of beta-amyloid.

Reference: Schupf N et al. Arch Neurol. 2007; 64(7): 1007-13.

Cognitive Capabilities Stabilize Before Decline to Alzheimer's Diagnosis

According to a recent study conducted by investigators at the Mayo Clinics in Rochester, Minnesota and in Jacksonville, Florida, progressively deteriorating cognitive capabilities often stabilize for several years before a final mental decline leads to a diagnosis of Alzheimer's disease (AD). Data on 199 subjects diagnosed with AD was analyzed and included information from 10 years prior to the diagnosis of AD and 5 years following the diagnosis. On average, the plateau began about 4 years prior to the AD diagnosis and lasted up until the final period of worsening cognitive ability. This plateau was better observed in memory function but not in the other 4 cognitive domains measured in this study.

Researchers stated that the observation of a pause in memory decline has important treatment implications. This plateau provides hope for a window of opportunity for neuronal rescue and/or behavioral intervention during an identifiable preclinical period.

Reference: Smith GE et al. Neurology 2007;69:133-139.

Increased BMI May Be A Risk Factor for Stroke

Increased body mass index (BMI) is a risk factor for both total and ischemic stroke according to analysis of data from a large Finnish cohort. The study was led by Gang Hu, MD, PhD, from the National Public Health Institute and the University of Helsinki in Finland. The Finnish cohort consisted of 49,996 Finnish men and women who were aged 25 to 74 years and free of coronary heart disease and stroke at baseline. The researchers investigated the association of BMI, waist circumference, and waist-hip ratio with total and ischemic stroke incidence among the group. On average, the subjects were followed-up for 19.5 years. During that time, 3,228 subjects (1,673 men and 1,555 women) had an incident stroke. Of these, 674 were hemorrhagic and 2554 were ischemic. After adjusting for age, study year, smoking status, physical activity, educational level, family history of stroke, and alcohol consumption, the researchers found that increasing BMI was a risk factor for total and ischemic stroke in both men and women when compared with individuals of normal weight.

Reference: Hu G et al. Arch Intern Med. 2007;167:1420-1427.

Visual Test May Distinguish Between Lewy Body Dementia and Parkinson's Disease Dementia

Delayed Matching to Sample (DMS-48), a newly introduced visual test, may help distinguish between dementia with Lewy bodies and Parkinson's disease dementia. Dr. Mondon of Universite Francois Rabelaise, Tours and colleagues studied 10 patients with Lewy body disease and 12 patients with Parkinson's disease dementia. The subjects underwent a battery of neuropsychological tests to assess verbal and visual memory (DMS-48), language, gnosia, praxia and executive functions. Patients with dementia due to Lewy body disease had poorer performances in orientation, Trail Making Test A and reading of names of colors in the Stroop Test. Their scores were also lower in the DMS-48 test in both immediate and delayed recognition. No differences were seen in other tests.

Reference: Mondon K et al. J Neurol Neurosurg Psychiatry 2007;78:738-741.

Socioeconomic Status May Play a Role In Stroke Recovery

Dr. Putman of Vrije Universiteit Brussel, Belgium and colleagues found certain socioeconomic factors played a role in the recovery of patients suffering from stroke. He used the Barthel Index and Rivermead Motor Assessment (RMA) to evaluate 419 stroke rehabilitation patients on admission, at discharge and 6 months after stroke. During the inpatient period, both measures indicated that patients with a low education level were about half as likely to improve when compared to those with higher education levels. However, there was no difference in recovery among groups with differing income levels. After discharge, those with a low income were considerably less likely to recover as gauged by scoring on the RMA for gross function, for leg and trunk function, and for arm function. There were no differences related to education.

Reference: Putman K et al. J Neurol Neurosurgery Psychiatry 2007;78:593-599.

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