

Mild Cognitive Impairment, Healthy Aging and Alzheimer's Disease

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As predicted in 1976, the growth of the elderly population has resulted in a tremendous increase in Alzheimer's disease (AD).¹ In 2007, there were probably more than 5 million Americans suffering from AD.² The major advances include more clinical tools to diagnose AD and several medications approved by the FDA for treatment.

Our goals are:

- Recognizing healthy, successful aging of cognition and developing strategies for primary prevention
- Developing new disease modifying agents to alter the course of AD.
- Defining mild cognitive impairment (MCI) as a diagnostic entity for early intervention.

HEALTHY AND SUCCESSFUL AGING

Healthy aging is defined by the lack of a significant decline in physical and mental abilities.³ These people are socially active and emotionally satisfied. One definition of "successful aging" is that the elderly who perform in the upper end of a distribution of test scores are deemed successful.⁴ The effect of aging on cognition is a hot topic. People older than 65 continue to change through the rest of their lives in different ways. A wide variety of age-related phenomena have been described.⁵ Many studies have documented various life styles leading to healthy or successful aging.^{3,4,5} Learning from these studies, preventive strategies are postulated to delay the onset of dementia. Among them, education and participation in certain leisure activities are two areas which have demonstrated benefit.^{6,7}

From epidemiological data, Katzman pointed out that elder people with poor or no education have an increased risk of developing dementia⁶ compared to those better educated. It is postulated that education might generate brain "reserve", which can compensate the initial presen-

tation of dementia.⁷ In a five-year, prospective, longitudinal study of healthy elderly adults (above 75 years of age), Verghese et al. reported that the elderly (n=345; age 78.9) who participated in three kinds of cognitive activities and one physical activity had a reduced risk of dementia.⁸ Reading, playing board games and playing musical instruments are deemed beneficial cognitive activities; dancing is the only physical activity identified that is associated with a lower risk of dementia. They also observed that subjects (n=124; age 79.7) who eventually developed dementia (the majority of them had AD) were older individuals with lower levels of education (less than 12 grades) and relatively lower test scores (on two memory tests) at baseline. This landmark study provides evidence of risk-reducing activities to delay the onset of AD.

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MILD COGNITIVE IMPAIRMENT (MCI)

The term, **mild cognitive impairment (MCI)**, was initially used as stage 3 of Reisberg's **Global Deterioration Scale (GDS)** in the staging of AD.⁹ Petersen, et al then proposed MCI as a diagnostic entity for the transition between normal aging and AD.¹⁰ In 2001, the American Academy of Neurology published its guideline for the diagnosis of MCI.¹¹ The criteria include 1) memory complaint 2) objective memory impairment 3) normal general cognitive function 4) intact ADLs 5) not demented by DSM IV criteria. The clinical tools recommended according to the guideline are the **Mini-Mental State Examination (MMSE)**, the **Clinical Dementia Rating (CDR)** scale

and other neuropsychological batteries, to be used as screening tests.

Clinicians encounter several pitfalls when diagnosing MCI. It is caused by a variety of pathologies other than just AD. To predict that a MCI patient is in the prodromal stage of AD, we have to consider other differential diagnoses. In the elderly, the two most common conditions which can mimic MCI are depression and stroke. Patients with late-life depression commonly complain of memory and cognitive problems. By sophisticated neuropsychological testing, their cognitive functions are usually within normal limits and subjective memory problem can be restored by adequate treatment. Older adults who had a sudden onset of cognitive impairment often had a cerebrovascular event. Recent studies have reported that patients with the amnesic-type of MCI often do have underlying AD pathology. For example, Morris has proposed that since so many amnesic MCI patients have AD pathology the diagnostic criteria need to be revised.¹² In contrast, the Mayo clinic reported that 71% of amnesic MCI brains displayed the AD pathology but that 29% of them showed non-AD pathologies, which particularly affected the mesial temporal regions.¹³

Neurochemical studies of MCI brains have demonstrated upregulation of the synthetic cholinergic enzyme, suggesting no decline of acetylcholine in MCI brains. This fits with the observation that all published clinical trials to date of cholinesterase inhibitors show no significant efficacy.¹⁴ Currently the FDA approves no treatment for MCI because all the data indicate a clear lack of benefit.

ALZHEIMER'S DISEASE

In the near future, we will witness major advances in the treatment of AD, such as the introduction of disease-modifying agents. None are yet available, however. The first crucial step in treating AD patients is to classify the clinical stage. (Figure 1). Today only symptomatic treatments are available for AD, including **cholinesterase inhibitors (CEIs)** and a **NMDA receptor**

Flow Chart of AD treatment

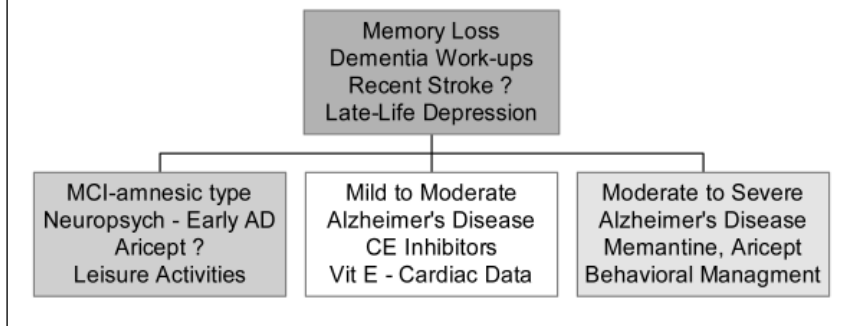


Figure 1.

antagonist. Since 1992, the FDA has approved five medications to treat Alzheimer's disease. We no longer prescribe tacrine because of significant side effects. Donepezil, rivastigmine and galantamine are approved for treating mild to moderate stage of AD. In 2004, memantine was approved for the moderate to severe stage of AD. In 2007, donepezil won approval for the severe stage of AD; rivastigmine has a skin patch approved to treat the mild to moderate AD.

In the clinic, patients can be evaluated simply by the MMSE as the first assessment tool. Many clinical scales have been developed to replace the MMSE. However, the MMSE yields a significant amount of data for interpretation. The first step in establishing the diagnosis of AD is to rule out other mimicking conditions, both treatable and untreatable. For example, a typical, high school-educated, 70 year-old patient comes in with a caregiver complaining of a memory problem, and scores 24/30. Based on the education level and age, the score suggests a high probability of dementia. Using a set of laboratory tests and a brain scan (CT or MRI), a clinician can confidently rule out other causes and establish AD as the cause of dementia (two-step approach). Scores of 12 to 23 are usually considered the mild to moderate stage of AD, as defined in the cholinesterase inhibitor clinical trials. A score below 15 indicates the moderate to severe range. However, there is no consensus about the defined score for the moderate stage of AD. The Alzheimer's Disease Cooperative Study (ADCS) group reported that the ability to perform a wide range of instrumental and basic ADLs correlates well with the MMSE scores of AD patients. A significant drop on the MMSE to below 20 correlates

with a significant decline in ADLs from the mild to moderate stage; likewise, a score below 15 indicates a further decline toward the moderate to severe stage.

Treating the cognitive problems of AD patients is limited to those approved by the FDA. When AD patients receive treatment, we should monitor progress of disease with the MMSE. A 4-point decline within a short period (6 months) deserves repeated clinical evaluation for other medical conditions which can worsen cognition. The combination of CEIs and memantine is recommended for treating the moderate to severe AD patient if side effects are tolerable. Memantine is not approved for mild AD or MCI diagnosis.

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Disclosure of Financial Interests

The author has no financial interests to disclose.

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