JAMDA 16 (2015) 1–5

JAMDA

journal homepage: www.jamda.com

Editorial

New Horizons in the Management of Alzheimer Disease

John E. Morley MB, BCh *

Divisions of Geriatric Medicine and Endocrinology, Saint Louis University School of Medicine, St. Louis, Missouri

Alzheimer disease remains a major disease in nursing home residents for which available medications produce minimal improvement.[1–5] No drugs have been found to be effective for the prodromal phase of dementia: mild cognitive impairment (MCI).[6] As has been regularly documented in your *Journal*, there are a number of behavioral and lifestyle approaches that can improve function and quality of life and decrease falls.[7–11] This editorial reviews the more recent findings in this area and also examines some of the exciting pharmacological innovations that may improve cognition in the future.

It is important to recognize that families and physicians commonly fail to recognize the presence of dementia.[12] This has led to development of a variety of formalized tests for cognition. Of these, the most commonly used was the Mini-Mental State Examination (MMSE), which has good sensitivity and specificity for dementia, but poor ability to recognize MCI.[13,14] Using the MMSE, Ferretti et al[15] found that a quarter of persons admitted to subacute care had dementia based on MMSE. Among these, 70% were newly diagnosed after admission to subacute care. The Brief Interview for Mental Status functions as well as the MMSE, and physicians need to be aware of this tool, which is included as part of the Minimum Data Set 3.0.[16,17] A quick bedside screen for dementia is to ask persons their age and date of birth.[18] Both the Montreal Cognitive Assessment and the St. Louis University Mental Status examination are excellent for recognizing MCI as well as dementia.[19–23] This is particularly important because many residents in subacute care, such as those with asthma,[24] cardiovascular disease,[25] and diabetes mellitus,[26–28] have MCI. Where there is doubt concerning the diagnosis, video conferencing with a geriatrician or geriatric psychiatrist has been shown to be helpful.[29] In addition, all residents in nursing homes should be screened for subsyndromal delirium using either the Confusion Assessment Methodology or "faces" technique.[30–32] Delirium superimposed on dementia results in worse outcomes.[33] The International Association of Geriatric and Gerontology nursing home initiative has stressed the importance of recognizing and providing support for all nursing home residents with cognitive dysfunction.[34–36]

Reversible Causes of Dementia in Nursing Home Residents

These are best remembered using the mnemonic "DEMENTIAS" (Table 1). Polypharmacy, especially when persons are receiving a number of drugs with anticholinergics or when the blood pressure is being excessively lowered, represents a major cause of cognitive impairment.[37–43] Antipsychotic use accelerates the chances of worsening dementia and increases mortality.[44–51] The first "E" stands for emotional, with the understanding that depression can result in a decline in cognitive function that was previously recognized as "pseudodementia."[52–54] Metabolic disorders, such as vitamin B12 deficiency, diabetes, and hypothyroidism, are classically associated with declining cognition. Declining hearing, including that associated with ear wax accumulation, also causes deficits in cognition.[55] Normal-pressure hydrocephalus is another treatable cause of dementia.[56] Its characteristics are a decline in cognition, gait disturbance, and incontinence. Tumors and other space-occupying lesions (eg, subdural hematomas) are another cause of dementia. A variety of infections can cause cognitive decline, either by direct infiltration of the brain or by increasing cytokine levels that cause decreased cognition.[56] There is increasing evidence that atrial fibrillation can cause vascular dementia and accelerate dementia that already exists.[57–59] Sleep apnea is a cause of cerebral hypoxia that leads to neuronal damage and cognitive decline.[60]

A Time to Focus on Behavioral and Lifestyle Changes

In persons in nursing homes, dementia is a predictor of walking ability, decline in function, and deaths.[61] Some of this may be due to the increased white matter lesions, representing vascular disease, seen in persons with dementia.[62] This may also be because physically frail persons have an increase in cognitive impairment.[63–70] These factors suggest that physical exercise could be a major therapy in persons with dementia.[71,72] Lam et al[72] found that Tai Chi for 1 year slowed the rate of cognition decline and depression for persons in the community and residential living centers in Hong Kong. Singh et al[73] recently showed that resistance exercises resulted in improved Alzheimer Disease Assessment Scale—Cognition and slowed decline in executive function. Exercise also has been shown to decrease difficult behavior expressions in nursing homes.[74–76] Exercise also will improve physical function in persons with frailty.[77–79]

Nutrition represents another area that can improve cognition.[9] Epidemiology studies have suggested that vitamin D may play an important role in cognition.[80–82] Vitamin D–binding protein combines with amyloid-beta to reduce its effects.[83] In addition, vitamin D can reduce oxidative damage in the brain. Much data now support the protective effects of a Mediterranean diet to reduce the risk of Alzheimer disease.[84,85] In mice, we showed that extra virgin olive oil improved cognition in an Alzheimer model.[86] The

* Address correspondence to John E. Morley, MB, BCh, Division of Geriatric Medicine, Saint Louis University School of Medicine, 1402 S. Grand Boulevard, M238, St. Louis, MO 63104.

E-mail address: morley@slu.edu.

http://dx.doi.org/10.1016/j.jamda.2014.10.022

Table 1
Reversible Causes of DEMENTIAS

Drugs: anticholinergic, antipsychotic, hypotension
Emotional: depression
Metabolic: vitamin B12 deficiency, hypothyroid, diabetes mellitus
Ears and visual deficits
Normal-pressure hydrocephalus
Tumors and other space-occupying lesions
Infection: sinus infections, HIV, syphilis
Atrial fibrillation
Sleep apnea

PREDIMED-NAVARRA study showed that an extra liter of olive oil a week improved memory over 6.5 years.[87] In addition, in community-living older persons, a Mediterranean diet reduced frailty.[88]

Epidemiological studies have suggested ingesting fish 2 to 4 times a week may improve cognition.[89,90] Similarly, the fish oils (docosahexanoic and eicosahexanoic acid) improve memory in Alzheimer models of mice.[91] However, studies giving humans fish oil have been disappointing.[92,93]

Persons with dementia who have an elevated body mass index tend to have better outcomes than those who are thinner.[94] Similarly, weight loss is associated with poor outcomes in older demented persons.[95–97] Classical nutritional supplements appear to have little effect on cognition.[98] Specific dietary supplements, such as "Souvenaid," have been shown to have mild effects on cognition in some studies.[99–101]

Computerized mind games have a small effect on cognition.[102,103] A list of these can be found in the *Journal* in the article by Anderson and Grossberg.[104] Similarly, there is some evidence of reminiscence therapy to improve cognition.[105,106] Robotic companions also have positive effects on quality of life of residents in nursing homes.[107–110] Although music therapy has some positive effects, it does not improve cognition.[111] Similarly, humor therapy can enhance quality of life in nursing home residents.[112] Gardens also appear to have a positive effect and may reduce agitation.[113] Alzheimer villages have been developed as an alternative to Special Care units, but despite the positive publicity, they have not yet been studied.[114–116] Similarly, the Eden Alternative, although much touted as a "change agent," has not been shown to have clear-cut effects in controlled studies.[117,118]

As previously outlined in an editorial in the *Journal*, cognition stimulation therapy is a highly effective therapy.[119] It improves quality of life and cognition.[120–122] In the nursing home, a pilot quality improvement study showed that cognition stimulation therapy coupled with physical exercise markedly improved cognition.[123] SAIDO (learning therapy) has been shown to effectively improve memory in nursing home residents in this issue of the *Journal*.[124] Another article in this issue explores the cost-effectiveness of cognition stimulation therapy.[125]

The results of the FINGER (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) were presented at the International Alzheimer's Association meeting in Copenhagen.[126] This was a 2-year study of 1260 participants aged 60 to 77 years who either received education or a carefully defined intervention. The intervention consisted of a Mediterranean diet, aerobic and resistance exercise, computer-based cognitive training, and social activity. The intervention group had a highly statistically improved cognition. This is in keeping with the epidemiological study of Verghese et al,[127] which showed that persons who read, play board games, play a musical instrument, or dance were associated with less dementia. All of these findings strongly support providing these interventions in the community and in nursing homes.

New Treatments on the Horizon

At present, most drugs for Alzheimer disease have failed.[128,129] This is especially true of those that lower amyloid-beta protein.[130] Amyloid-beta protein in high doses blocks memory formation.[131,132] However, at low doses our group has shown that amyloid-beta is a physiological enhancer of memory.[133,134] Thus, it is not surprising that totally inhibiting the production of amyloid-beta eventually leads to worsening of cognition. The situation of amyloid-beta is similar to that of thyroxine, in which high levels lead to disease (hyperthyroidism) but so do low doses (hypothyroidism).

The SAMP8 mouse is a natural mutation resulting in an age-related amyloid-beta protein-mediated model of cognitive impairment.[135–138] Originally, we showed that antibodies to amyloid-beta enhanced memory in these mice but only short term.[139–141] For this reason, we developed a phosphorothioate 42-mer antisense to amyloid precursor protein (APP). Antisenses are molecules that block the ability of messenger RNA to direct the production of proteins. The APP antisense decreased acquisition and memory in the SAMP8 mice and also in the transgenic Tg2576 mouse, which overproduces human APP.[142,143] In addition, it reduced oxidative damage in the brain, reversed the damage in the brain and reversed the damage to the blood brain barrier.[144,145] These antisenses cross the blood brain barrier and can be administered intranasally.[146] Antisenses do not wipe out production of APP. More recently, we have produced other antisenses to presenilin and GSK3β, which have similar effects to the antisense to APP.[147,148] Others have produced an antisense to tau protein,[149] an antisense to SOD, which can be given safely to humans.[150] It would appear that these antisenses may be leading contenders for the treatment of Alzheimer disease.

Alpha-lipoic acid is a potent antioxidant that improves memory and decreases oxidative damage in a mouse model of Alzheimer disease.[145,151] A single study suggests it may improve memory in humans.[152] Unfortunately, in mice it increases mortality.[153]

There have been a number of animal studies showing that stem cells can improve memory in Alzheimer disease rodent models.[154,155] The exact method by which stem cells improve memory is uncertain. It is unlikely to be by cell replacement, as the stem cells survive for only a short time in the brain. Stem cells may provide trophic support to brain cells. These "rejuvenating" factors produced by stem cells include nerve growth factor, brain-derived neurotrophic factor, vascular endothelial growth factor, glial cell line–derived neurotrophic factor, and insulinlike growth factor-1. It is also possible that they modulate inflammation by producing interleukin-10, an anti-inflammatory cytokine. Finally, by showing microglia-like activity, they may clear amyloid-beta plaque. A single human study using cells enriched to produce nerve growth factor can be administered to humans and show potentially an improvement in neurogenesis.[156]

Parabiosis (joining the circulations) of a young and old animal has been shown to enhance neurogenesis in the older mouse.[157] This is predominantly due to a circulating growth-derived factor (GDF11). This has led a group in Stanford to undertake a study to give transfusions from young persons to persons with Alzheimer disease.[158]

There are studies showing that insulin given intranasally may improve memory in humans.[159] Glucagonlike peptide I, pioglitazone, and metformin enhance memory and are candidates to improve memory by altering the effects of insulin in the brain.[160–162] Our preliminary data suggest that metformin improves memory by stopping BAX translocation to the mitochondria and thus preventing increased permeability of the mitochondrial membrane leading to apoptosis.

Bioavailable testosterone has been shown to be a powerful predictor of cognitive decline in men.[163–165] The SAMP8 mouse has low