Dementia: The Role of Alternative Therapies

Marwan Sabbagh MD, FAAN
Chief Medical-Scientific Officer
Director of Clinical Research
Sun Health Research Institute
Failing Memory: The Problem

- AD is the 7th leading cause of death in the US
- AD affects 5.1 million Americans
- AD is the leading cause of long term care placement and accounts for up to 60% of LTC Insurance claims
- $100 billion is spent annually in the US for AD related costs and expenses
- By 2010, AD will affect one in ten over age 65 and the cost of care will raise to $160 billion
Summary of Prevalence and Impact of AD on Societal Costs

• > 100,000 people die from AD per year
• It is estimated that 14 million Americans will have AD by the year 2050
• A cost of $45,000 per patient per year
• Alzheimer’s patients/families spend > $200,000 over the remainder of the patient’s life
• >50% of nursing home residents have Alzheimer’s disease

## Incidence of Common Neurological Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Incidence (per 100,000)</th>
<th>New Cases (per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia</td>
<td>268</td>
<td>670,000</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>188</td>
<td>470,000</td>
</tr>
<tr>
<td>Stroke</td>
<td>200</td>
<td>500,000</td>
</tr>
<tr>
<td>Seizures</td>
<td>50</td>
<td>124,000</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>16</td>
<td>40,000</td>
</tr>
<tr>
<td>Primary neoplasm</td>
<td>15</td>
<td>37,500</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td>6</td>
<td>15,000</td>
</tr>
<tr>
<td>Primary brain tumor</td>
<td>6</td>
<td>15,000</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>2</td>
<td>5,000</td>
</tr>
<tr>
<td>Gullain Barre’</td>
<td>1</td>
<td>2,500</td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>0.3</td>
<td>750</td>
</tr>
</tbody>
</table>
Differential Diagnosis of Dementia

- Alzheimer’s Disease (AD)
- Dementia with Lewy Bodies (DLB)
- AD & Vascular Dementia (mixed)
- Vascular Dementia
- Frontotemporal Dementia (FTD)
- Parkinson’s Disease
- Huntington’s Disease
- Other Degenerative Diseases (PSP, OPCA, ALS with dementia)
- Dementias Secondary to Alcohol
- Depression/Pseudodementia
- Normal Pressure Hydrocephalus (NPH)
- Structural Lesions
- Metabolic Disorders (Hypothyroidism)
- Infections (e.g. neurosyphilis, AIDS, CJD)
- Drug Intoxication
Risk Factors for Cognitive Decline

- age
- genetic influences
- ApoE status
- female gender
- medical comorbidities
Risk Factors for Cognitive Decline:

**Medical Comorbidities**

- Hypertension
- Heart disease
- Diabetes
- Elevated low-density lipoprotein cholesterol
- High homocysteine levels
- Transitory ischemic attacks (TIAs)
- Head trauma
- Environmental exposure to toxins (particularly lead)
Risk Factors for Cognitive Decline: Psychological/Psychosocial Factors

- Low educational achievement
- Lack of physical activity
- Lack of social interaction/leisure activities
- Excessive response to stress (excessive cortisol levels)
Risk Factors for Cognitive Decline: Lifestyle Choices

- Smoking
- Substance abuse, including alcohol and illicit drugs
Alzheimer’s and the Brain
Phosphorylated tau in tangles

Total tau in neuronal axons

Aβ_{1-42} in senile plaques
Amyloid Precursor Protein (APP)

- A single membrane-spanning protein, which has a large extracellular amino terminal domain and small intracellular cytoplasmic domain

- Undergoes regulated intramembrane proteolysis via membrane-bound proteases

\( \alpha, \gamma \) Secretase Pathway: No A\( \beta \) Formation

- Cleavage is catalyzed by \( \alpha \) and \( \gamma \) secretases, respectively, producing sAPP\( \alpha \), p3 peptide, and an APP intracellular domain (AICD).
**Secretase Pathway: Aβ**

- Cleavage is catalyzed by β and γ secretases
- The γ cleavage site is within the transmembrane
Beta-Amyloid

Enzymes
Beta-Amyloid Plaque
γ Secretase

- An aspartyl protease complex composed of APH1, nicastrin, PS1 or PS2, and PEN2
- Cleaves APP following APP scission by β secretase
- Site of cleavage is variable and can occur after Aβ\textsubscript{38}, Aβ\textsubscript{40}, or Aβ\textsubscript{42}
  - Site of cleavage determines self-aggregating potential and pathogenicity of Aβ
  - Aβ\textsubscript{42} has strong propensity to oligomerize in vivo

**Aβ Oligomers and Aβ Plaques: Theories on Neurotoxicity**

- Which Aβ form is toxic to the neuron?
  - Aβ oligomers
    - Induce synaptic dysfunction?\(^1\)
    - Decrease hippocampal plasticity?\(^1,2\)
  - Aβ plaques
    - By-product of AD only?\(^3\)
    - Interferes with dendritic signal transmission?\(^4\)

---

β-amyloid – The Core of the Senile Plaques

Amyloid Precursor Protein (APP)

Extracellular

Lipid Membrane

β-secretase

γ-secretase

α-secretase

Aβ 40

Aβ 42

Soluble forms

β Pleated Sheet

Senile Plaque

Relkin, 2006.

Amyloid Angiopathy
β-Amyloid–related disease-modifying strategies

APP gene

APP

Aβ Monomer

Aβ Oligomer

Aβ Fibril

Fibrillogenesis modulators

Deposition

Diffuse Plaque

Senile Plaque

Anti-inflammatory

Production

Aggregation

Immuno-therapy

Relkin, 2006.

Cu++ Chelator

Antisense

Secretase modulators

secretase modulators

Modulators
γ Secretase Inhibition

Plasma

Liver clearance

Blood-brain barrier

CSF

Interstitial space

Brain

CSF=cerebrospinal fluid.
Increased Aβ Production

Decreased Aβ Clearance

Increased Aβ Monomers, Oligomers, and Fibrils

Aβ Plaque Deposition

Synaptic Dysfunction

Neuronal Death, Atrophy of the Cortex, Hippocampus, and Amygdala

• Progressive, irreversible brain disorder which is not a part of normal aging\(^1\)
• Insidious onset of early symptoms often mistaken for age-related memory change\(^1\)
• Disease progression leads to behavioral and cognitive changes\(^1\)
• Variable disease progression and rate of decline\(^1\)
• Risk factors: aging, family history\(^1\), head injury\(^2\)

MCI=mild cognitive impairment.
What can you do?
Maintain Your Brain: Make brain healthy life choices

- Be heart smart
- Adopt a brain healthy diet
- Stay physically active
- Stay mentally active
- Alzheimer’s prevention starts now!
Be Heart Smart

- Optimize blood pressure control. (Certain types of diuretics, beta blockers and dihydropyridine Ca^{++} channel blockers)
- Don’t smoke
- Reduce homocysteine levels
- Keep diabetes under control. (SQ Insulin and insulin sensitizing medications are being explored as treatments)
- Reduce your cholesterol and saturated fat intake
- Control your body weight: midlife obesity doubles risk of dementia. A meta analysis shows that obesity increase OR between 1.1 and 3.0
Adopt a Brain Healthy Diet

- Reduce intake of foods high in fat and cholesterol
- Consume a diet rich in dark vegetables and fruits (high in anti-oxidants): kale, spinach, brussel sprouts, alfalfa, sprouts, broccoli, beets, bell pepper, onion, corn and eggplant. Fruits include prunes, raisins, blueberries, blackberries, strawberries, raspberries, plums, oranges, red grapes, and cherries
- Eat fish high in Omega 3 fatty acids: halibut, mackerel, salmon, trout, and tuna
- Adopt the Mediterranean diet
Stay Physically Active

- Physical exercise is essential to maintaining good blood flow.
- It reduces risk of secondary comorbid events (MI, CVAs, and diabetes)
- Exercise may increase neurotrophic activities
- A sustained regimen is more effective than a high endurance regimen
- Don’t box! Boxing significantly increases risk for developing AD
- Avoid head injuries: wear protective headgear
Stay Mentally and Socially Active

• Keep your brain active every day.
  – Commit to lifelong learning
  – Work crossword puzzles
  – Attend lectures and plays
  – Take courses
  – Play games: bridge and other card games
  – Try memory exercises

• Mentally stimulating activities strengthen brain cells

• Remaining socially active reduces stress

• Social activity is mentally engaging (volunteer, travel)
Goals for the Treatment of AD

- Improve Memory
- Improve Behavioral Symptoms
- Slow Progression
- Delay Onset
What about?

- Prescription medications
- Estrogen
- Anti-inflammatory
- Vitamins
- Supplements
Prescription Medications

- Cholinergic agents (Aricept, Exelon, and Razadyne) work by increasing acetylcholine in the brain. All have broad spectrum efficacy. Approved for mild to moderate AD.
- NMDA antagonist (Namenda) blocks a certain type of receptor that is over-stimulated in AD to restore normal function. It is approved for moderate to severe AD.
- These medications can be used in combination.
Development of Alzheimer Pharmacotherapy

**Symptomatic Treatment**
- **Nootropics**
  - Tacrine
  - Donepezil
  - Rivastigmine
  - Galantamine
  - Memantine

**Pre-1980s**
- Idiopathic
- Neurochemical Deficit Cholinergic Hypothesis

**1980s**
- Systemic Deficiency Amyloid Hypothesis
- Cholinesterase Inhibitors

**1990s**
- Anti-inflammatory
- Hormone Replacement
- Anti-oxidants (Vitamin E)
- NMDA Antagonists

**2000s**
- Anti-amyloid Agents
- Immunotherapy

**2010s**
- Protein Misfolding Modified Amyloid Hypothesis

**FDA Approved**
- 1993
- 1997
- 2000
- 2001
- 2003

Relkin, 2006.
Estrogen and AD

- Several epidemiological studies show that HRT delays onset of AD
- *In vitro*, estrogen has trophic effects on neurons and improves APP processing in a positive manner
- Several well-designed studies demonstrate no significant benefit on cognition or progression in post-menopausal women with AD (Munnard et al. JAMA 2000, Wang et al. Neurology 2000, Henderson et al. Neurology 2000)
- Early WHI and WHIMS studies inconclusive. All adverse events occurred in the progesterone treated group.
- Follow-up WHI and WHIMS data show no protective effects of HRT against the development of AD.
- PREPARE also does not show risk reduction
- Disparate findings might be accounted for by methodology
Anti-Inflammatories and AD

- Inflammation found in brains of AD
- Epidemiology suggests a decreased risk of AD in NSAID users (Zandi et al. 2002 and others)
- Indomethacin first NSAID studied. Results equivocal because of high attrition rate (Rogers et al. 1993)
- Diclofenac/misoprostol showed no benefit on progression and had a high dropout rate
- Prednisone not effective (Aisen et al. 2000)
- Naproxen vs Rofecoxib trial completed. Both ineffective in treating AD (Aisen et al. 2002)
- The prevention trial with NSAIDs (ADAPT) has found that naproxen reduces risk in long term follow-up better than celecoxib but with more treatment related adverse events.
AD Therapy: Future

- Prevention strategies (NSAIDs, estrogen, gingko biloba)
- Immunotherapy (active and passive)
- New cholinesterase inhibitors (Huperzine A, phenserine, Dimebon)
- Cholesterol lowering agents (atorvastatin, simvastatin)
- Anti-aggregation agents (tramiprosate, others)
- Gamma secretase modulates (Tarenflurbil, others)
- Gamma secretase inhibitors (LY-450139, MK-0249)
- Neuroprotection (Divalproex sodium)
- Chelating agents (clioquinol, PBT2)
- Diabetic medications (insulin sensitizers)
- sRAGE inhibitors (TTP/Pfizer)
- Serotonin agonists (Xaliproden, others)
- Nicotinic receptor agonists (ABT089 and others)
- TNFalpha blockers (entanecept and others)
# Current Prevention Trials in AD

<table>
<thead>
<tr>
<th>Trial (Acronym)</th>
<th>Status</th>
<th>Intervention</th>
<th>Subject selection criteria</th>
<th>Duration (years)</th>
<th>Overall incidence rate (% per year)</th>
<th>Planned sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREPARE</td>
<td>Stand-alone</td>
<td>Estrogen or Estrogen + Progestin</td>
<td>Female sex, Family history of AD, Age &gt; 65</td>
<td>3</td>
<td>5</td>
<td>900</td>
</tr>
<tr>
<td>ADAPT</td>
<td>Stand-alone</td>
<td>Naproxen or Celecoxib</td>
<td>Family history of dementia, Age &gt; 70</td>
<td>5 - 7</td>
<td>3 - 3.4</td>
<td>2,800</td>
</tr>
<tr>
<td>SYST-EUR</td>
<td>Add-on</td>
<td>Nitrendipine and/or Enalapril and/or Hydrochlorothiazide</td>
<td>Systolic hypertension, Age &gt; 60</td>
<td>5 *</td>
<td>1.6</td>
<td>3,000</td>
</tr>
<tr>
<td>GEMS</td>
<td>Part add-on</td>
<td>Ginkgo biloba</td>
<td>Age &gt; 75</td>
<td>5 **</td>
<td>4</td>
<td>3,000</td>
</tr>
<tr>
<td>WHIMS</td>
<td>Add-on</td>
<td>Estrogen or Estrogen + Progestin</td>
<td>Female sex, Age &gt; 65</td>
<td>6***</td>
<td>2</td>
<td>8,300</td>
</tr>
<tr>
<td>PREADVISE</td>
<td>Add-on</td>
<td>Vitamin E or Selenium or Both</td>
<td>Age &gt; 62 or &gt; 60 (if of African or Hispanic ancestry)</td>
<td>9-12</td>
<td>1</td>
<td>10,700</td>
</tr>
</tbody>
</table>
Memory loss and Alzheimer’s is a big concern for Baby Boomers

- A survey of 1000 baby boomers finds that they are clearly not ready emotionally, physically, or financially to deal with AD in their own future.
- Those surveyed stated they have little confidence that policymakers, the US healthcare system, and drug regulators are prepared to help.
- The vast majority are extremely concerned about the potential impact of Alzheimer’s on their health, quality of life, and finances as well as on the healthcare system.
- 90-95% of respondents said they would either be unprepared or find life “not worth living”.
- 80% of respondents said their savings would not be sufficient to cover the cost of care.
- Only 8% feel that current treatment options are adequate. In fact, 80% are willing to take experimental treatments that have the potential for stopping the disease and preserving their quality of life.
- 82% of respondents remained unsure about what the government is doing to prioritize Alzheimer’s; 84% feel that more should be done; 75% feel that Alzheimer’s should be a top priority.
Supplements That Focus on Cognitive Health and Protection compelling evidence of protective qualities or benefit

- Ginkgo biloba
- Omega-3 Fatty Acids (DHA)
- Curcumin
- Huperzine A
- Phosphatidylserine
Supplements with less robust evidence of protection or benefit

- Choline
- Lecithin (phosphotidylcholine)
- DHEA
- Acetyl-L-carnitine
- DMAE
- Vinpocetine
- Grapeseed extract and quercetin
- Resveratrol
Huperzine A

- Huperzine A is a potent inhibitor of the enzyme acetylcholinesterase (AChE), as it was discovered in China.
- Huperzine, like prescription AChE inhibitors on the market for Alzheimer’s, preserves acetylcholine levels in the brain.
- Huperzine has anti-oxidant and neuroprotective properties.
- It is used in China to treat Alzheimer’s.
- Huperzine is currently in clinical trials in the US as a treatment for Alzheimer’s disease.
Docahexaenoic Acid (DHA)

- DHA is concentrated in neuronal synapses, making it a vital player in the communications between brain cells, or neuronal signal transduction.
- DHA has anti-inflammatory properties that may be the protective mechanism that inhibits or slows the development of Alzheimer’s.
- In multiple controlled studies, mice fed dietary omega-3 FAs, including DHA, displayed marked superiority in learning and memory than those mice that weren’t fed these fatty acids.
- In transgenic mice, treatment with DHA has resulted in lower amounts of the toxic beta amyloid protein in the brain.
- Patients already diagnosed with Alzheimer’s have lower levels of DHA as well as lower levels of the Omega-3 fatty acids.
- Martek’s synthetic DHA is being investigated in clinical trials as a treatment for AD.
Phosphatidylserine (PS)

- PS may be important for Alzheimer's prevention and treatment because it restores acetylcholine release in aging rats by maintaining an adequate supply of the molecule. Its presence also increases the availability of choline for new acetylcholine production.
- PS has demonstrated some usefulness in treating cognitive impairment, including Alzheimer's disease, age-associated memory impairment and some non-Alzheimer's dementias.
- Several double-blind studies suggest that PS can help maintain cognitive function in older individuals and may be able to improve memory and learning skill in some.
- In the largest multicenter study to date of PS and Alzheimer's disease, 142 subjects aged 40 to 80 were given 200 milligrams of phosphatidylserine daily or placebo over a three-month period. Those treated with PS exhibited improvement on several items on the scales normally used to assess Alzheimer's status. The differences between placebo and experimental groups were small but statistically significant.
Curcumin

- Epidemiological studies showing that India has one of the lowest prevalence rates of AD in the world have led some researchers to look closer at curry consumption as a possible Alzheimer’s-fighting tactic.
- Curcumin’s marquee property is probably its anti-oxidant action. Several laboratory experiments have shown that curcumin may have even more potent anti-oxidant properties than vitamin E.
- In the lab, scientists have demonstrated that curcuminoids, but not vitamin E, protected cells from injury induced by toxic beta amyloid protein and inhibited the formation and extension of amyloid fibrils in transgenic mice.
- Its anti-inflammatory effects may be the medium through which curcumin could slow Alzheimer’s pathology. Recent studies have looked especially closely at curcumin’s anti-inflammatory role in comparison to NSAIDs. Investigators have demonstrated that curcumin works just like and is as strong as ibuprofen and naproxen.
- Clinical trials are underway at UCLA investigating encapsulated curcumin as a treatment for AD.
Resveratrol

- Resveratrol is found in red wine.
- Resveratrol is a naturally occurring phytoalexin produced by some higher plants. Phytoalexins are chemical substances produced by plants as a defense against infection by microorganisms, such as fungi.
- Resveratol has been shown to have anti-cancer, antiviral, neuroprotective, anti-aging, anti-inflammatory, and life-prolonging effects.
- Resveratrol has recently been reported to be effective against neuronal dysfunction and cell death.
- When applied to Alzheimer's disease, a recent study in the Journal of Biological Chemistry suggests that resveratrol markedly lowers the levels of secreted amyloid peptide produced in different cells. While resveratrol did not stop the production of amyloid, it did promote the degradation of the amyloid by activating the enzyme proteosome to break down other proteins.
- Since amyloid protection and plaque formation occurs years before people manifest Alzheimer's symptoms; long-term preventive intake of resveratrol might enhance the clearance of the amyloid peptide before it ever takes root in the form of a plaque, and thus delay or even prevent the onset of AD.
Gingko Biloba

- Gingko biloba is one of the most popular and widely-studied brain supplements in the world.
- Ginkgo extract is standardized to contain 24% of flavonoids, which were found to be beneficial in maintaining cognitive health in large epidemiological studies.
- Ginkgo has also been shown to have, in varying degrees, beneficial effects on memory and concentration,
- In 1997, the *Journal of the American Medical Association* reported some stabilization of cognitive decline in Alzheimer’s and vascular dementia patients [LeBars et al 1997].
- A prevention trial, the Ginkgo Evaluation of Memory Study (GEMS), is currently underway with results expected within 2 to 3 years.
- In a study from Pacquid, France, dietary intake of flavonoids was associated with a 50 percent cut in risk developing dementia over the course of five years.
- Another study showed that dietary consumption of flavonoids was associated with a 46 percent risk reduction for developing Alzheimer’s.
Folic acid

- In the literature, folic acid is the only vitamin whose isolated total intake has been significantly associated with a lowered risk of Alzheimer’s.

- Reduced folate has been directly linked to elevated homocysteine levels, beta amyloid accumulation, and increased DNA damage in transgenic mice over-expressing APP. Folic acid deficiency and elevated homocysteine levels impair DNA repair in brain cells responsible for memory, the hippocampal neurons, and make these brain cells vulnerable to amyloid toxicity in experimental Alzheimer’s models.

- Low folate status is associated with poor cognitive function and dementia in the elderly, whereas the literature suggests that supplement-delivered folic acid may confer some protective effect for Alzheimer’s risk.

- In the Baltimore Longitudinal Study of Aging, participants who took folic acid at or above 400 mcg had a 55 percent risk reduction for developing Alzheimer’s.

- In a recently published study from north Manhattan, the subjects taking the highest dose of Folic Acid had a 50% reduction of AD risk compared to subjects taking the lowest dose. The highest dose on average exceeded 488mcg daily.

- Clinical trials completed in 2008 using 4800 mcgs as a treatment for AD showed no positive benefit.
Vitamin C and E

- Vitamin C, or ascorbic acid, is probably the most-consumed stand-alone vitamin on the market today. Studies have demonstrated its antioxidant, anti-atherogenic, anticarcinogenic, antihistamine, antiviral, antihypertensive properties.

- Vitamin C and brain function: it may modulate prostaglandin synthesis to favor the production of eicosanoids with antithrombotic and vasodilatory activity. The possible sparing and regeneration of alpha-tocopherol by vitamin C could be yet another factor in the vitamin's possible anti-atherogenic action.

- According to PDRhealth (2007) there are several mechanisms of proposed neuroprotective effects of vitamin E: antioxidant as a principal lipid antioxidant and participates in signal-transduction. Vitamin E involved with functions of neuronal cell membranes.

- Vitamin E levels in food and plasma were found to be inversely associated with incident Alzheimer's disease in three prospective studies.

- One of many prospective studies of older individuals in Utah found reduced risk of Alzheimer's among vitamin E and vitamin C supplement users as well. At baseline, taking both vitamin E and vitamin C supplements in combination reduced the risk of having Alzheimer's by almost 80 percent. When this association was re-assessed after three years, using both vitamin E and vitamin C supplements in combination still reduced the risk of AD by 64 percent. Taking either vitamin individually did not seem to be as protective.