Non-pharmacologic treatment
Nonpharmacologic treatment for Alzheimer’s Disease (AD)

Good physical health = Great aging brain

☑ Regular physical exercise
☑ Positive emotions
☑ Positive relationships
☑ Limiting chronic stress

“Memory and the Aging Brain.” Steven W. Anderson, PhD
Thomas J. Grabowski, Jr. MD The University of Iowa. June 2003
Exercise prevents the chronic stress-adaptation failure in AD

- Aerobic exercise training increases brain volume in aging humans


How do health problems affect my brain?
## AD risk factors

<table>
<thead>
<tr>
<th>Fixed Risk Factors</th>
<th>Modifiable Risk Factors</th>
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<tbody>
<tr>
<td>Age</td>
<td>Lack of exercise</td>
</tr>
<tr>
<td>Family history</td>
<td>Smoking</td>
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<tr>
<td>Genetics</td>
<td>High blood pressure and heart disease</td>
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<tr>
<td>Mild Cognitive Impairment (MCI)</td>
<td>High cholesterol</td>
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<td></td>
<td>Poorly controlled diabetes</td>
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<td>Low education</td>
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FDA-approved Medications for Alzheimer’s Disease
Cholinesterase inhibitors (ChEI)
Donepezil, Rivastigmine, Galatamine

ChEIs prevents the enzyme destruction of the neurotransmitter acetylcholine (Ach)

– Acetylcholine declines in AD; loss of cholinergic input to the cortex from the basal forebrain.

– **Donepezil:**
  • selective acetylcholinesterase inhibitor

– **Rivastigimine & Galatamine:**
  • Inhibitor of acetylcholinesterase & butyrylcholinesterase.

Cholinesterase inhibitors (ChEI)

**Galatamine:** (ER capsule), 8mg x 4 wks, 16mg x 4 wks, then 24mg thereafter. Take w food. Also as BID dose.

**Rivastigmine:** Also FDA approved for dementia in Parkinson’s disease/ Lewy Body Disease. (Capsule) 1.5mg BID x 2 wks, 3.0mg BID x 2 wks, 4.5 mg BID x 2 weeks, then 6.0 mg BID thereafter. Take with food. (Transdermal patch): 4.6 mg q 24hrs (5 cm2 size =9 mg), then increase to 9.5mg/24 hrs after 4 weeks (10 cm2 size=18 mg).

**Donepezil:** 5 mg daily x 4-6 weeks then increase to 10mg; may increase to 23mg after 12 weeks. FDA has been petitioned to rescind 23mg formulation.

Memantine (Noncompetitive glutamate N-methyl-D-aspartate (NMDA)-receptor blocker)

- FDA approved for moderate-severe AD.
- Blocks the NMDA receptor calcium channels, inhibiting the sustained, low-level influx of excitatory calcium ($\text{Ca}^{2+}$) ions into postsynaptic glutamatergic neurons.
- May have a neuroprotective effect by preventing the negative consequences of persistent activation of the neuron.
- Dose 5mg/day wk1, 5mg BID wk2, 5mg qam and 10mg qpm wk 3, 10mg bid thereafter. ER available.

Combination Therapy: Memantine + Cholinesterase inhibitors

- NIH-sponsored analysis of 382 patients over the course of 15 years
- Study supports combination therapy: Memantine + Cholinesterase inhibitors

NIH = National Institutes of Health.
Investigational drugs and vitamin therapies
<table>
<thead>
<tr>
<th>DRUG</th>
<th>MECHANISM OF ACTION</th>
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<tbody>
<tr>
<td>AN1792 Vaccine</td>
<td>Abeta immunotherapy</td>
</tr>
<tr>
<td>Tramiprosate alzhemed - homotaurine</td>
<td>Abeta aggregation inhibitor</td>
</tr>
<tr>
<td>Latrepiridine (Dimebon)</td>
<td>Mitochondrial stabilizer – originally anti-histamine</td>
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<tr>
<td>Tarenflurbil (Flurizan)</td>
<td>Gamma-secretase modulator</td>
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<tr>
<td>Semagacestat</td>
<td>Gamma-secretase inhibitor</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Possible membrane lipid modifier</td>
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<tr>
<td>Docosahexaenoic acid (DHA)</td>
<td>Possible membrane lipid modifier or antioxidant</td>
</tr>
<tr>
<td>B12, B6 , Folic Acid, Vitamin E, Omega-3 fatty acids, Ginko Biloba</td>
<td>Multiple theories, negative longitudinal studies</td>
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Statins: HMG CoA reductase inhibitors

Cholesterol Biosynthesis Pathway

- Acetyl CoA + Acetoacetyl-CoA → HMG CoA → Mevalonate

HMG CoA Reductase

↑

Isopentenyl Pyrophosphate

↓

Geranyl Pyrophosphate

↓

Prenylated Proteins

Farnesyl Pyrophosphate

↓

Bile salts, Vit D, Steroids

Cholesterol

← Lanosterol ← Squalene

Fig. 1. Cholesterol biosynthesis.
Evidence shows elective statin use may reduce AD progression:
- Hyperlipidemia promotes Aβ production and deposition in animal models of AD and cholesterol reduction reduce Aβ deposition.

Large clinical trials show no efficacy in delaying progression but NO increased AD risk.

Feb 2012: FDA warned that statins could cause “fuzzy” thinking or reversible memory loss.

The evidence: USE statins for patients with heart or cerebrovascular disease (regardless of AD status)

Siegel GJ et al. Statin therapy is associated with reduced neuropathologic changes of AD. Neurology 2008;71:383
“Eat less and exercise more? That’s the most ridiculous fad diet I’ve heard of yet!”
Vitamins versus diet/ lifestyle

• Diet rich in antioxidants and vitamins beneficial but NOT pills/ supplements!

• Vitamin E 😞
  – No difference between placebo
    • High doses increase stroke risk
    • Increased relative risk of prostate cancer in men

• Homocysteine lowering therapy (B-vitamins) 😞 Folic Acid B6, B12 – no benefit with supplements
  – The vitamins lower the homocysteine level but little else.
  – B12 and folic acid supplementation did not have any statistically significant effect

Ford et al. Vitamins B$_{12}$, B$_{6}$, and folic acid for cognition in older men Neurology 2010;75:1540-1547.
Vitamins versus diet/ lifestyle

- **DHA** 🙁 - Docosahexaenoic acid is an omega3 polyunsaturated fatty acid found in fish.
  - component of synaptic plasma membranes
  - In animals models, DHA may affect the rate of signal transduction, be neuroprotective.
  - NEGATIVE RCTs: no effect with supplementation.
- **Ginko biloba** 🙁
  - marketed as a supplement that prevents or delays cognitive decline
  - VERY LARGE Randomized controlled trials were negative
  - A numerically greater number of subjects treated with *ginko* developed dementia as compared to placebo

Quinn JF et al. JAMA 2010;304:1903-1911.
**Anti-inflammatory agents**

- Observational study showed daily ibuprofen use (>5 YEARS) suppressed amyloid beta 1-42 production, decreased the risk of AD by 25-40%.
  - However, there was an increase risk of serious adverse events (GI bleeding, other bleeding events).
  - Animal experience indicated that NSAIDs reduce brain inflammatory markers such as activated microglia and may reduce brain deposits of Aβ.
- No significant benefit found with prednisone, diclofenac, rofecoxib, nimesulide or naproxen. COX-2 inhibitors and nonacetylated agents not effective.


Insulin Resistance and AD

- Risk factor for AD: Type II diabetes
  - Impaired insulin signaling in AD, contributing to the neurodegenerative process.

- Exendin-4 (or Exenatide)
  - Phase II trials: testing the effects of novel enzyme-resistant analogues of the insulin-releasing incretin hormone, glucagon-like peptide 1 (GLP-1).

- Intranasal Insulin
  - Delayed memory was improved in the MCI group receiving 20 IU of insulin ($P < .05$). Among insulin-treated participants, no improvement in biomarkers.

Caffeine may decrease level of beta-amyloid in AD transgenic mice

- AD mice received the equivalent of 5 cups coffee/day for 2 months
- End result: caffeinated AD mice performed as well as normal mice
- Caffeinated mice brains showed ~50% reduction in beta amyloid
- Researchers suggested that caffeine suppresses inflammatory changes in the brain that lead to an overabundance of beta amyloid.
"The most common side effect of this medication is a loss of disposable income."
The Cole Neuroscience Clinic mantra is...

...what's good for your BRAIN is good for your heart.
Alzheimer’s Disease Education and Referral Center
800-438-4380
http://www.nia.nih.gov/alzheimers

Government Web site
http://www.clinicaltrials.gov

Alzheimer’s Tennessee
http://www.alztennessee.org