Dementia and Cognition in Older Adults: Year in Review 2008 2009

Advances in Internal Medicine

May – June 2009
Methodology

• Clinically important for practicing internists (or good for dinner parties)
• Methodologically sound
• Review in ACP Journal Club or Journal Watch in addition to primary journal
• Topics: Cognition/Dementia, Medication use
Memory Enhancement

"As I get older, I find I rely more and more on these sticky notes to remind me."
Which of the following interventions has been shown to enhance memory in older adults?

A. Ginkgo biloba  
B. Vitamin B6, B12, and folate  
C. Caloric restriction  
D. Aspirin  
E. None of the Above
Caloric Restriction and Memory

- Caloric restriction (CR) has been shown to increase life span in multiple species
- Some evidence suggests that CR might also be beneficial for the “aging brain”
- In addition, specific micronutrients might be beneficial for the aging brain
- 50 healthy elders (mean age = 61) recruited to participate in study
  - 19 participants reduced caloric intake by 30%
  - 20 participants were instructed to increase unsaturated fatty acids in diet
  - 10 patients served as control

*Witte et al Proc Nat Acad Sci USA 2009; 106: 1255*
Witte et al Proc Nat Acad Sci USA 2009; 106: 1255
Witte et al Proc Nat Acad Sci USA 2009; 106: 1255
Conclusions and Caveats

• Small trial

• This is not really a dementia trial, it’s a cognitive enhancement trial in older adults

• However, along with other research, suggestive that caloric restriction may do some good things to the aging process

• Even for the most motivated among us, this is hard to adhere to
Does Ginkgo prevent AD?

- Ginkgo biloba did not prevent AD
  - 3000 patients with no impairment or MCI
  - Randomized to 120 ginkgo daily v. placebo
  - 6 years of follow up
  - No differences in diagnosis of dementia
  - Slightly higher risk of hemorrhagic CVA with ginkgo

*JAMA 2008: Nov 19; 300: 2253*
Does Homocysteine Lowering Prevent Dementia?

- Homocysteine elevation is associated with vascular dysfunction, high plasma amyloid.
- 400 patients age 76+ and mild-moderate AD randomized to combination of B6, B12, and folate or placebo.
- 18 month follow up.
- Homocysteine lower in the treatment group; no difference in other outcomes.
- Treatment group had more depressive symptoms.
- Similar results in a meta-analysis published last year.

*JAMA 2008 Oct 15; 300: 1774*
*Arch Intern Med 2007 Jan 8: 167:21*
Does Aspirin Prevent Dementia?

- Cardiovascular Disease is associated with cognitive decline in older aged people
- Researchers in Scotland randomized 3000 people between age 50 and 75 to 100mg daily of ASA or placebo
- Patients ad moderate CV risk with ABI of <0.95
- At five years, no differences in summative cognitive scores in multiple domains

*BMJ 2008 Sep 1; 337: 1198*
Does CABG lead to long term cognitive decline?

A. Yes, multiple studies have demonstrated that bypass surgery poses particular risks for long term cognitive decline

B. No, CABG poses risks for short term cognitive decline, but no more than other surgeries (POCD)

C. No, but patients who are likely to receive CABG are at risk for long term cognitive decline

*Ann Neurology 2008 May; 63: 547
*Ann Neurology 2008 May; 63: 581
Does CABG lead to long term cognitive decline?

• CAD/atherosclerosis are risk factors for both vascular dementia and AD

• CABG has been associated with cognitive decline in some studies (“CABG- head”), but lack of control groups have limited ability to interpret findings (CABG or CAD?)

• Johns Hopkins researches did neuropsych testing on 150 patients undergoing CABG and 90 patients undergoing PCI or medical management

• Slight differences at baseline

Ann Neurology 2008 May; 63: 547
Ann Neurology 2008 May; 63: 581
Does CABG lead to long term cognitive decline?

- Mild cognitive decline seen in both groups at 5 years; no differences between groups

*Ann Neurology 2008 May; 63: 547
Ann Neurology 2008 May; 63: 581*
<table>
<thead>
<tr>
<th>Cognitive Domains</th>
<th>Difference in Change from Baseline to 72 Months</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Difference$^a$ (95% CI)</td>
<td>$p$</td>
</tr>
<tr>
<td>Verbal Memory</td>
<td>0.01 ($-0.23$, 0.26)</td>
<td>0.94</td>
</tr>
<tr>
<td>Visual memory</td>
<td>0.10 ($-0.25$, 0.44)</td>
<td>0.58</td>
</tr>
<tr>
<td>Visuoconstruction</td>
<td>0.02 ($-0.24$, 0.28)</td>
<td>0.88</td>
</tr>
<tr>
<td>Language</td>
<td>$-0.07$ ($-0.26$, 0.13)</td>
<td>0.48</td>
</tr>
<tr>
<td>Motor speed</td>
<td>0.20 ($-0.03$, 0.43)</td>
<td>0.10</td>
</tr>
<tr>
<td>Psychomotor speed</td>
<td>$-0.10$ ($-0.32$, 0.13)</td>
<td>0.36</td>
</tr>
<tr>
<td>Attention</td>
<td>$-0.02$ ($-0.30$, 0.26)</td>
<td>0.89</td>
</tr>
<tr>
<td>Executive function</td>
<td>$-0.13$ ($-0.48$, 0.22)</td>
<td>0.47</td>
</tr>
<tr>
<td>Global</td>
<td>0.02 ($-0.15$, 0.18)</td>
<td>0.80</td>
</tr>
</tbody>
</table>

$^a$Difference numbers that are positive indicate that the coronary artery bypass grafting (CABG) group had greater change than the nonsurgical cardiac comparison group.

$^b$Statistically significant values.

CI = confidence interval.
Bottom line

- Reassuring that CABG might not have as much impact on cognition as formerly thought
- However, control group was not perfectly matched with CABG group, and possibility of confounding exists
- Transient syndrome of POCD well described in surgical patients, and may last for 3 months or more

Ann Neurology 2008 May; 63: 547
Ann Neurology 2008 May; 63: 581
Do Severe Hypoglycemic Episodes increase the risk for dementia?

- Recent studies (ACCORD, ADVANCE) have raised questions about the role of tighter glucose control in DM type II
- Researchers asked question of role of recurrent hypoglycemia on risk of incident dementia
- Longitudinal cohort study of 16,667 patients mean age of 65 with DM type II
- Hypoglycemia diagnoses from ED and discharge diagnoses
- Adjusted for multiple potential confounders

Whitmer et al JAMA April 15, 2009
Participant Characteristics

- Mean age 65-66, 55% men
- 60% white, 11% AA, 11% Hispanic
- Time since first DM dx: ~ 15 years
- 61% CAD, 96% HTN, 3% ESRD
- HgbA1C 8.1
- Mix of diet, oral hypoglycemics, insulin

Whitmer et al JAMA April 15, 2009
<table>
<thead>
<tr>
<th>Any Hypoglycemia</th>
<th>Dementia</th>
<th>No Dementia</th>
<th>Incidence Rates per 10,000 person-years</th>
<th>Attributable risk per year %</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>10%</td>
<td>90%</td>
<td>328</td>
<td>2.4% (CI 1.7-3.0)</td>
</tr>
<tr>
<td>Yes</td>
<td>17%</td>
<td>83%</td>
<td>567</td>
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</table>

_Whitmer et al JAMA April 15, 2009_
<table>
<thead>
<tr>
<th># of hypoglycemia episodes</th>
<th>Dementia</th>
<th>No Dementia</th>
<th>Incidence Rates per 10,000 person-yrs</th>
<th>Attributable risk per year %</th>
</tr>
</thead>
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<tr>
<td>0</td>
<td>10%</td>
<td>90%</td>
<td>328</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>15%</td>
<td>85%</td>
<td>492</td>
<td>1.6 (0.9-2.4)</td>
</tr>
<tr>
<td>2</td>
<td>22%</td>
<td>78%</td>
<td>762</td>
<td>4.3 (2.4-6.3)</td>
</tr>
<tr>
<td>3 or more</td>
<td>20%</td>
<td>80%</td>
<td>755</td>
<td>4.3 (2.1-6.4)</td>
</tr>
</tbody>
</table>
Bottom Line

• As patients with diabetes become older, think carefully about the risks/benefits of tight glycemic control, particularly in patients who are having episodes of hypoglycemia
"Because of your age, I'm going to recommend doing nothing."
Which of the Following is true about use of antipsychotics in patients with Dementia?

A. Research has consistently shown that haloperidol and other traditional antipsychotics pose a higher risk for adverse outcomes than newer atypical antipsychotics

B. It is recommended that all patients get an ECG prior to initiation of antipsychotic therapy

C. It is recommended that all patients get an ECG before and after initiation of antipsychotic therapy

D. Antipsychotics should not be used to treat patients with dementia
Antipsychotics & Dementia

- Researchers identified 90,000 patients between age 30 and 74 who used antipsychotic drugs between 1990 and 2005
- About half used typical agents (haloperidol, thioridazine and half used atypicals (clozapine, quetiapine, olanzapine, risperidone)
- Matched to 200 controls
- Both typical and atypical agents roughly doubled the risk for sudden cardiac death
- Higher dose conferred higher risk

*NEJM 2009 Jan 15; 360: 225
NEJM 2009 Jan 15; 360: 294*
More on Antipsychotics

- Researchers in the UK compared CVA incidence within patients during periods on/off antipsychotic drugs
- Compared dementia patients to non-dementia patients
- Exposure to ANY antipsychotic increased the risk of CVA
- In patients with dementia: RR 3.5
- In patients without dementia RR 1.4
- Rate ratios decreased back to 1 about 5 months after drug discontinued

*BMJ 2008 Aug 28; 337a1198*
Antipsychotics & Dementia

165 elderly patients in UK with dementia on antipsychotics for at least 3 months randomized to continue their antipsychotic or receive placebo

- Followed for 12 months
- Primary outcome: Mortality at 12 months
- Antipsychotics used: thioridazine, trifluoroperazine, haloperidol, clorpromazine, or risperidone

NEJM 2009 Jan 15; 360: 225
NEJM 2009 Jan 15; 360: 294r
Number at risk (deaths)

Continue treatment  29 (3)  26 (7)  13 (3)  7 (1)  3 (0)
Placebo         34 (1)  33 (1)  19 (5)  11 (0)  7 (1)

Log-rank p = 0.03
Antipsychotics: Conclusions and Recommendations

• Best estimates are that the NNH for antipsychotics in dementia is 300 (for one excess death per year)

• Editorialists recommend:
  – Using antipsychotics as infrequently as possible in dementia patients
  – Disclose Risks (“Black Box”)
  – Use behavioral strategies and consider other medication types first (though evidence base low)
  – Obtain ECG before/after prescribing to look for QTc prolongation
  – Try drug discontinuation frequently
Which of the following medications has been shown to improve cognitive outcomes to the greatest degree in patients with dementia?

A. Donepezil

B. Transdermal rivastigmine

C. Memantine

D. Dimebon
Are you depressed yet?

Here’s one glimmer of hope....
Dimebon

- Dimebon is a medication formerly used in Russia as a non-selective antihistamine
- Found to inhibit acetylcholinesterase, weakly block NMDA receptor signalling, and inhibit mitochondrial permeability
- Neuroprotective properties found for both AD and Huntington’s disease
Dimebon

- Researchers in Russia studied its potential as a medication for treatment of AD
- 188 patients with mild-moderate AD randomized to dimebon or placebo
- 160 patients completed the first six months of treatment; 90% of them entered a second six month observation period; 90% of them completed the full trial (N = 155)
- Adverse events similar in the two groups

*Lancet 2008 July 19; 372: 207*
<table>
<thead>
<tr>
<th></th>
<th>Week 26</th>
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<tbody>
<tr>
<td></td>
<td>Dimebon (n=89)</td>
</tr>
<tr>
<td>ADAS-cog</td>
<td>-1.9 (-2.92 to -0.85)</td>
</tr>
<tr>
<td>NHAISE</td>
<td>1.8 (1.14 to 2.39)</td>
</tr>
<tr>
<td>ADCS-ADL</td>
<td>1.3 (-0.09 to 2.70)</td>
</tr>
<tr>
<td>NPI</td>
<td>-1.0 (-2.62 to 0.56)</td>
</tr>
<tr>
<td>CIBIC-plus</td>
<td>3.7 (3.52 to 3.91)</td>
</tr>
</tbody>
</table>
MMSE
P<0.001

ADCS-ADL
P<0.005
Conclusions and Caveats

- In this trial, dimebon looks more effective than both acetylcholinesterase inhibitors and memantine
- Side effects were minor, = with placebo
- A phase III clinical trial is now being conducted
New Horizons

Cookson & Hardy
NEJM 12/21/2006
Other medications on the horizon

- Phase 2 trial of gamma secretase inhibitor published last year (Ann Neurol 2008)
- Intravenous immunoglobulin (IVIg). A phase III clinical trial is testing whether IVIg antibodies can modify the course of mild AD.
- Rember, a novel form of the dye methylthioninium chloride in a phase II trial.
- The peptide AL-108, given by nasal spray, in a phase II clinical trial for amnestic MCI.
- PBT2, a metal-protein-attenuating compound prevents interaction of beta-amyloid with copper and zinc in a phase II clinical trial in people with early-stage AD.
If you want to read more….

2008 CMAJ Series on Dementia

- Part 1: Risk assessment and primary prevention of Alzheimer disease Feb 26;178:548-56
- Part 2: Diagnosis March 25; 178: 825-36
- Part 3: Mild Cognitive Impairment May 6; 178
- Part 4: Approach to the Management of Mild-Moderate Dementia Oct 7; 179: 787-93
- Part 5: Nonpharmacologic and pharmacologic therapy for mild to moderate dementia Nov 4; 179: 1019-26
- Part 6: Management of Severe AD Dec 2; 179: 1279-87