Updates on Dementia Prevention, Diagnosis, and Care

Advances in Internal Medicine 2011

Clinical Questions to be addressed:

- Should we be screening for Dementia?
- What is the best screening tool for dementia in primary care?
- Can we do anything to prevent the onset of memory problems or slow decline once present?
- What are the role of biomarkers in the diagnosis and treatment of dementia?
- This will not be a comprehensive review of dementia

Why is This Important?

- Prevalence of Dementia:
  - 1% at age 60
  - Doubles every five years
  - 30-50% by age 85
- Aging of the Baby Boomers
- If dementia could be delayed by 5 years, the prevalence would be cut in half

Disclosures

Bree Johnston has no relationships with any proprietary entity producing health care goods or services consumed by or used on patients.

(much to the regret of her playwright husband)
Before you get depressed…

- Some aspects of memory get better with age
  - Vocabulary
  - Crystallized intelligence
  - Wisdom?

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Should We Screen?

- USPSTF:
  - The U.S. Preventive Services Task Force concludes that the evidence is insufficient to recommend for or against routine screening for dementia in older adults.
  - The Task Force therefore could not determine whether the benefits of screening for dementia outweigh the harms.
  - USPSTF 2003

- If we screen, should we screen for dementia or MCI?
Diagnosis of MCI

- Memory impairments beyond what would be expected for age
- Deficits not severe enough to meet criteria for dementia
- About 1/3 of patients with MCI will develop dementia

Diagnosis of Dementia

- Multiple cognitive deficits manifested by impaired memory plus:
  - Impaired language or
  - Apraxia or
  - Agnosia or
  - Impaired executive function
- Deficits:
  - Significant enough to impair function
  - Interferes with work or social activities
- Not delirium

Rationale for Screening

- Advance care planning
- Protection of assets
- Public health safety (driving)
- Helps guide management of comorbidities
- Initiate medications early
  - No evidence that this improves outcomes
  - If this changes, would argue for screening for MCI
Public records show a 93-year-old man found frozen to death in his Michigan home had received several utility shut-off notices… six letters were sent to Marvin Schur’s home in the past two years. His body was found Jan. 17, several days after Bay City Electric Light & Power restricted electricity and a month after his final shut-off notice. Records suggest Schur was confused about how to pay. He tried at least twice to pay bills at his bank, which couldn’t accept them.

See also Widera JAMA 2011

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What is the best screening test for MCI?
1. The MMSE
2. The Mini-cog
3. Trails B
4. The MOCA
5. The Sweet 16
The Mini-Cog

- 3 item recall + Clock Drawing Test (CDT)
  - Give 3 items and ask pt to repeat and remember them
  - Divert using CDT (10 minutes after 11)
  - Ask for recall of 3 words
  - CDT Normal if the patient places the correct time (1 point) and the clock appears grossly normal (1)

Sensitivity 76-97%
Specificity 89-95%

Borson S et al. JAGS 2003; 51: 1451-54.
The Mini-cog must be followed up!

- Many practitioners in the field currently prefer the MOCA (Montreal Cognitive assessment) to the MMSE.
- More sensitive than MMSE for MCI.
- No copyright restrictions.
- Scoring 0-30.
- http://www.mocatest.org/
- Remember that any cognitive test needs to be used in combination with clinical and historical information to make a diagnosis of dementia.

Montreal cognitive assessment: MoCA

PERMISSION TO USE THE MoCA©
http://www.mocatest.org/

CLINICAL USE
Universities/Foundations/Health Professionals/Hospitals/Clincs/Public Health Institutes:
MoCA may be used, reproduced, and distributed WITHOUT permission.
The test should be made available free of charge.
Written permission and Licensing Agreement is required if funded by commercial entity or pharma.
The areas under ROC curves were compared with the method of Delong and Clarke-Pearson (1988) for correlated curves. The difference was statistically significant: $\chi^2(1, N=182)=11.66, p<0.001$.

ROC for distinguishing Normal Controls from MCI.

**MoCA scores**

<table>
<thead>
<tr>
<th></th>
<th>Normal Controls (NC)</th>
<th>Mild Cognitive Impairment (MCI)</th>
<th>Alzheimer’s Disease (AD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>90</td>
<td>94</td>
<td>93</td>
</tr>
<tr>
<td>MoCA average score</td>
<td>27.4</td>
<td>22.1</td>
<td>16.2</td>
</tr>
<tr>
<td>MoCA standard deviation</td>
<td>2.2</td>
<td>3.1</td>
<td>4.8</td>
</tr>
<tr>
<td>MoCA score range</td>
<td>25.2 – 29.6</td>
<td>19.0 – 25.2</td>
<td>21.0 – 11.4</td>
</tr>
<tr>
<td>Suggested cut-off score</td>
<td>$\geq$26</td>
<td>$&lt;26$</td>
<td>$&lt;26$</td>
</tr>
</tbody>
</table>

*Although the average MoCA score for the AD group is much lower than the MCI group, there is overlap between them. The suggested MoCA cut-off score is thus the same for both. The distinction between AD and MCI is mostly dependent on the presence of associated functional impairment and not on a specific score on the MoCA test.*

**Sensitivity and Specificity (%) MoCA and MMSE**

<table>
<thead>
<tr>
<th>Cut-off</th>
<th>Normal Controls</th>
<th>Mild Cognitive Impairment</th>
<th>Alzheimer’s Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\geq$26</td>
<td>100</td>
<td>18</td>
<td>78</td>
</tr>
<tr>
<td>&lt;26</td>
<td>87</td>
<td>90</td>
<td>100</td>
</tr>
</tbody>
</table>

**ARCHIVES OF INTERNAL MEDICINE**


**Development and Validation of a Brief Cognitive Assessment Tool: The Sweet 16**

Tamara G. Fong, MD, PhD; Richard N. Jones, ScD; James L. Rudolph, MD, SM; Frances M. Yang, PhD; Douglas Tommet, MS; Daniel Habtemariam, BA; Edward R. Marcantonio, MD, SM; Kenneth M. Langa, MD, PhD; Sharon K. Inouye, MD, MPH
Sweet 16 Items

Table 2. Description of Sweet 16 Items

<table>
<thead>
<tr>
<th>Item No.</th>
<th>Item Description</th>
<th>Cognitive Domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-8</td>
<td>Orientation to time and place</td>
<td>Temporal/Spatial</td>
</tr>
<tr>
<td>9-11</td>
<td>Immediate repetition (3 items)</td>
<td>Registration</td>
</tr>
<tr>
<td>12-13</td>
<td>Digit span backward</td>
<td>Sustained attention</td>
</tr>
<tr>
<td>14-16</td>
<td>Recall (3 items)</td>
<td>Short-term memory</td>
</tr>
</tbody>
</table>

SWEET 16 INSTRUMENT

1. What is the year? Score                   1
2. What is the date? Score                   1
3. What is the day of the week? Score       1
4. What is the month? Score                  1
5. Can you tell me where we are? (What is the name of this place?) Score 1
6. What city are we in? Score                1
7. What state are we in? Score               1
8. What floor of the hospital are we on? (What room of the house are we in?) Score 1

9-11. I am going to name 3 objects. After I have said them, I want you to repeat them. Remember what they are because I am going to ask you to name them again in a few minutes. The three items are: "APPLE", "TABLE", "PENNY" (PRESENT WORDS CLEARLY AND SLOWLY. WORDS MAY BE PRESENTED UP TO 4 TIMES, BUT SCORE ONLY ITEMS REPORTED AFTER FIRST PRESENTATION)

APPLE Score 1
TABLE Score 1
PENNY Score 1

TOTAL SCORE: ____________/10

Receiver operating curve for the Sweet 16 (S16) and the Mini-Mental State Examination (MMSE) scores compared with clinical diagnoses

The Case of the Disappearing Sweet 16

- PAR asked Sharon Inouye to take Sweet 16 off the Hospital Elder Life (HELP) Website
- Both PAR and Sweet 16 authors declined to speak about the “sensitive issue”
- Follow the link for details, http://en.wikipedia.org/wiki/Mini-mentalstate_examination#Copyright
- Says blogger Jim Amos “I think what happened is PAR may believe the Sweet 16 is similar enough to the MMSE-2 BV to justify enforcing copyright”

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Bottom Line

- The rationale for screening for dementia/MCI is sound, but not proven to improve outcomes
- Mini-cog is a good initial screen for dementia
- Should be followed up with another test, such as the MOCA
- Stay tuned for the copyright saga of the Sweet-16, which may succumb to copyright laws

Your new patient is a 70 year old who is healthy. She wants your advice on what she can do to reduce her chances of getting dementia. She has osteoarthritis, but is otherwise healthy. She is widowed, lives in a retirement community, and is active playing golf and volunteering. Her medications are aspirin, acetaminophen, glucosamine, and vitamins D and E. Her physical exam is normal.
What would be most likely to prevent dementia in her?

1. Drink 1-2 glasses of red wine daily
2. Do Tai Chi 3 times weekly
3. Do regular housework
4. Do regular cognitive exercises
5. Ingest 2000 IU vitamin D daily

An Aside….
This area can be confusing because there are at least 5 different types of literature:
- What factors enhance cognition?
- What factors reduce cognitive decline?
- What factors prevent dementia (AD and/or other dementias)?
- What factors prevent MCI from progressing to dementia?
- What factors help people with dementia?

NIH State-of-the-Science Conference Preventing Alzheimer’s Disease and Cognitive Decline
April 26–28, 2010
Bethesda, Maryland

Annals of Internal Medicine; June 15, 2010, 152: 792-796

Problems with the Literature
- Most evidence is observational and not of high quality
- Difficulty differentiating between AD and vascular dementia
Non modifiable risk factors for AD

• Age
• Genetics
  – Gene mutations 5%
  – Apoe4 allele
• Female Gender

Lifestyle factors and AD

• Protective
  – Educational attainment
  – Cognitive activities
  – Participation in physical activities
• Harmful
  – Current smoking
  – Never having been married
  – Low social support
  – (Traumatic Brain Injury)

Nutritional Factors and AD

• Protective
  – Adequate folic acid intake
  – Longer chain omega 3 fatty acids
  – Low to moderate EOTH
  – High fruit and vegetable consumption
  – Low saturated fat consumption

Medical Factors and AD

Increased Risk of AD

• Diabetes
• Elevated blood cholesterol (in midlife)
• Depression
Possibly protective
• Use of statins (controversial)
Statins and AD

- 5 well done population based observational studies have suggested that statins may have a protective effect on development of dementia
  - Protective role for patients < age 80?
- However, RCTs of statins in dementia have been negative
- Also patients with vascular disease treated with statins have not shown cognitive benefits

Haan JAGS 2010

Statins And AD

- 3392 members of HMO age 65+ without dementia at baseline
- Statin use determined from pharmacy database
- Average of 6.1 years of follow up
- 263 patients developed probable dementia

HR for statin use = 0.62 (0.40-0.97)
HR for statin use < 80 = 0.44 (0.25-0.78)
HR for statin use > 80 = 1.22 (0.61-2.42)

Li et al JAGS 2010

Factors with inconsistent evidence

- Multiple vitamins
- Fatty acids
- Metabolic syndrome
- Blood pressure
- Plasma homocysteine levels
- Obesity and BMI
- Antihypertensive medications
- NSAIDs
- Gonadal steroids
- 15 cohort prospective trials including 30,331 individuals followed for 1-12 years
  - 38% reduced risk of cognitive decline in subjects with high levels of physical activity
  - 35% reduced risk for low to moderate levels of physical activity

Physical Activity and Dementia Incidence
- Meta-analysis of prospective studies of physical activity and incident dementia & AD
  - 16 studies of 163,797 non-demented adults at baseline, 3,219 incident cases at follow up
  - RR of dementia in highest vs lowest activity group = 0.72 (P<0.001); AD 0.55 (p<0.01)
  
Hamer 2009

MCI and Dementia
- Studies on physical activity in patients with MCI mixed
  Miller Int J Neurosci 2010
  Baker 2010
- Physical activity associated with improvements in neurobehavioral symptoms in patients with dementia in some studies, but impact on cognition much less clear
  Aman 2009
  Williams 2007

Physical Activity and Dementia: Summary
- Higher levels of physical activity appear to be associated with a reduced risk of cognitive decline and dementia, and may improve some aspects of cognitive function
- Unclear how much exercise helps once MCI and dementia established, although it may help some neurobehavioral symptoms in patients with established dementia
So what can you tell your patient?

Do:
- Exercise
- Cognitive activities
- Statins?, if indicated
- Some alcohol
- Folate, low saturated fat, fruits and vegetables, fish
- Possibly omega – 3 fatty acids
- Get married

Don’t:
- Smoke
- Let your spouse die
- Get depressed
- Get DM or metabolic syndrome or HTN

Results

<table>
<thead>
<tr>
<th>Interval</th>
<th>All Subjects Hazard Ratio (95% CI)</th>
<th>P Value</th>
<th>APOE ε4 Carriers Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil vs. placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First 12 mo</td>
<td>0.42 (0.24–0.76)</td>
<td>0.004</td>
<td>0.14 (0.06–0.31)</td>
<td>0.003</td>
</tr>
<tr>
<td>First 24 mo</td>
<td>0.64 (0.44–0.95)</td>
<td>0.03</td>
<td>0.54 (0.35–0.86)</td>
<td>0.009</td>
</tr>
<tr>
<td>All 36 mo</td>
<td>0.80 (0.57–1.13)</td>
<td>0.21</td>
<td>0.66 (0.44–0.98)</td>
<td>0.04</td>
</tr>
<tr>
<td>Vitamin E vs. placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First 12 mo</td>
<td>0.83 (0.52–1.32)</td>
<td>0.43</td>
<td>0.78 (0.49–1.24)</td>
<td>0.37</td>
</tr>
<tr>
<td>First 24 mo</td>
<td>0.93 (0.67–1.26)</td>
<td>0.79</td>
<td>0.93 (0.64–1.34)</td>
<td>0.79</td>
</tr>
<tr>
<td>All 36 mo</td>
<td>1.02 (0.74–1.41)</td>
<td>0.91</td>
<td>0.95 (0.66–1.36)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

* CI denotes confidence interval. P values were not adjusted for multiple comparisons. In the donepezil group, when corrected for multiple comparisons, the P value at 24 months for all subjects became nonsignificant (P=0.001), and the P value at 36 months for APOE ε4 carriers also became nonsignificant (P=0.078).
Love those British!

- There is no clear evidence that any intervention can prevent or delay the onset of dementia.
  Consensus Statement from British Assn. Psychopharmacology 2010

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Who should get biomarker testing for dementia risk assessment?

1. All patients over the age of 65
2. All patients with MCI
3. All patients with a family history of dementia
4. All patients with suspected AD
5. None of the above
What is the role of biomarkers?

- 10-20% of patients thought to have AD lack AD pathology at autopsy
- When treatments become more directed and effective, early accurate diagnosis will become more important
- Three recent articles have looked at different biomarkers for AD

Yaffe JAMA 2011
Clark JAMA 2011
Mattson JAMA 2009

Peripheral biomarkers

- About 1000 patients from Health ABC studied
- At baseline, were 70-79 years old and independent in ADLs
- Average of 9 years of follow up
- Patients underwent serial cognitive testing and had plasma β A42/40 levels measured

Yaffe et al JAMA 2011

Peripheral biomarkers

- Lower plasma β A42/40 was found to be associated with greater cognitive decline in elderly patients without dementia over 9 years
- Stronger correlation in those with less cognitive reserve

Yaffe et al JAMA 2011
CSF Biomarkers

- 2 part study
  - Part 1: Cross sectional study of patients with AD and controls to identify cut points for CSF $\beta$ A42, T-Tau, and P-Tau
  - Part 2: Prospective cohort study of patients with MCI followed for 2 years or until progression to dementia
  - Outcomes: sensitivity, specificity, positive and negative LR for CSF $\beta$ A42, T-Tau, and P-Tau

Results

- When used on patients with MCI, the combination of CSF $\beta$ A42/T-Tau ratio and T Tau identified incipient AD with:
  - 83% sensitivity
  - 72% specificity
  - LR + 3.0
  - LR – 0.24

Mattsson, N. et al. JAMA 2009;302:385-393

Copyright restrictions may apply.
Clinical implications

• Not ready for prime time – yet!

• May become important when AD specific treatments come along

• Some patients may want this information for future planning

Alzheimer’s diagnostic guidelines
April 19, 2011

Three distinct stages of Alzheimer’s disease:

• Preclinical – In some people, amyloid buildup can be detected with positron emission tomography (PET) scans and cerebrospinal fluid (CSF) analysis. These biomarkers are not ready for use by clinicians

• Mild Cognitive Impairment (MCI) – These tests may be applied in specialized clinical settings

• Alzheimer’s Dementia – Biomarker test results may be used in some cases to increase or decrease the level of certainty about a diagnosis of Alzheimer’s dementia, even as the validity of such tests is still under study

Nortin Hadler: Health Care Blog

“there is a great public health danger in prematurely using biomarkers in clinical practice for diagnosis or prognosis.”

“[I]t offers no advantage to our patients today. Rather it is far more likely to engulf the patient in spurious inferences at great personal expense. Biomarkers have been tested only in small and highly selected groups of patients where they have impressive rates of false positive results. That portends a great deal of over-diagnosis in less selected patients. Furthermore, all biomarker tests are expensive, some very expensive, and some have medical risks. None is near ready to be used in routine clinical practice.”

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www.alz.org/research/diagnostic_criteria
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Love those British!
• Cholinesterase inhibitors are effective for mild to moderate AD (A) and memantine for moderate to severe AD (A).
• Neither cholinesterase inhibitors nor memantine are effective in those with MCI (A).
• SSRIs may help behavioural (but not cognitive) features of FTD (B).
• Cholinesterase inhibitors can improve neuropsychiatric symptoms in Dementia with Lewy Bodies (A). Cholinesterase inhibitors and memantine can produce cognitive improvements in DLB (A).
• There is no clear evidence that any intervention can prevent or delay the onset of dementia.
Consensus Statement from British Assn. Psychopharmacology 2010

ACOVE Indicators for Dementia Care
• Assess cognition
• Review meds
• New Dementia
  – Neuro Exam
  – Depression screen
  – Lab Tests
• Management
  – Assess Function
  – Discuss AcHI
• Management (cont’d)
  – Behavioral symptoms
  – Manage behaviors
  – Risks/benefits of antipsychotics
  – Driving counseling
  – Specifying surrogate
  – Counseling caregiver
  – Alz Assn referral

Donepezil – Aricept ~$260/month
  Begin 5mg daily, increase Q 4-6 weeks
  Maximum 10mg daily
  Some new data on 23mg daily

Galantamine – Razadyne ~$100/month
  Begin 4 mg BID, increase Q 4 wks
  Maximum 12 mg BID

Rivastigmine – Exelon ~$260/month
  Begin 1.5 mg BID, increase Q2 wks
  Maximum 6mg BID

Rivastigmine Patch ~$240/month
  Maximum 9.6mg/24h
Summary

- Screening for dementia is important, and will become more important as treatments improve
- Mini-cog, MOCA, and Sweet 16 are all good screening tests
- Dementia – not preventable but some promising data
- Biomarkers – not ready for prime time