Disclosure

- Clinical trials
  - Pfizer-ADCS
  - Baxter-ADCS
  - Elan-Wyeth
It all boils down to this...

Good Brain  Bad Brain
OVERVIEW

- Dementia
  - DSM-IV criteria
  - Medical causes of dementia
  - Impact on the health care system

- Alzheimer’s Disease
  - History
  - Pathology
  - Clinical features
  - Genetics
  - Treatment

- Non-AD Dementias: VaD, DLB, FTD

- Future directions
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- **Non-AD Dementias: VaD, DLB, FTD**
Dementia

- Memory and at least one other cog domain involved
- Impaired general cognitive function
- Social, educational, occupational function impaired
- No medically reversible cause found

DSM-IV Criteria
AAN practice parameter: Diagnosis of dementia

- CT or MRI indicated for initial workup (Guideline)
- No evidence supporting volumetrics, PET, or SPECT (Guideline)
- APOE or other genetic tests not recommended (Guideline)
- Depression should be screened for (Guideline)
- B12 deficiency should be screened for (Guideline)
- Hypothyroidism should be screened for (Guideline)
- Screening for syphilis is not justified in most cases (Guideline)
- CSF analysis only recommended for 14-3-3 screen of suspected CJD (Guideline)

Knopman et al, Neurol 2001;56:1143-53
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Reversible Causes of Dementia

- V-subdural hematoma, reversible posterior leukoencephalopathy
- I-Syphilis, HIV, PML
- T-trauma, NPH, drugs
- A-SLE, Sjogren’s, MS
- M-Thyroid, Wernicke’s, Wilson’s, SCD (B12)
- I-Vasculitis, Hashimoto’s
- N-neoplasm, limbic encephalitis
- S-nonconvulsive status (EPC)
Medical problems causing memory loss are common in our normal research subjects.

Clinical cause of MCI following Medical evaluation per AAN practice parameter:

- Probable degenerative
- B12 deficiency
- Thyroid dysfunction
- Vascular
- NPH
- SDH
Drugs Associated with Cognitive dysfunction

- Benzodiazepines: valium, ativan
- NSAIDs: ASA, ibuprofen, indomethacin, naproxen, sulindac
- Antidepressants: TCAs, SSRIs
- Anticonvulsants: PHT, VPA, CBZ, PHB
- Antihypertensives: B-blockers, Ca-channel blockers
- H2 receptor antagonists: cimetidine, ranitidine
- Antibiotics: Cephalexin, metronidazole, fluoroquinolones
- Anticholinergics: Benztropine, trihexiphenidyl
- Antiarrhythmics: disopyramide, quinidine, tocanaide, amiodarone
- Antiparkinson agents: L-DOPA, pergolide, bromocriptine
- Muscle relaxants: Baclofen, cyclobenzaprine, methocarbamol
- Others: antihistamines/decongestants, digoxin, steroids, narcotics
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Alzheimer’s Disease: An Impending Public Health Care Crisis

1990: 3.8 million
2020 (est.): 5.6 million
2050 (est.): 10.2 million

- 65-74 years
- 75-84 years
- 85+ years

Latest CDC National Vital Statistics Reports (April, 2006): AD is 8th leading cause of death in US
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History

- 1906 - first description of Auguste D. age 51
- 1985 - NINDS-ADRDA criteria developed
  - Still used today
- 1991 - Flicker described MCI (preclinical AD)
- 1999 - MCI (preclinical AD) popularized by Mayo team
- 2007 - New criteria proposed

Alois Alzheimer 1864-1915

German neuropathologist & psychiatrist who described in 1906 the clinical and neuropathological features of a woman aged 51 years, with atrophied cerebral cortex, senile plaques and neurofibrillary tangles
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Alzheimer’s disease (NINDS-ADRDA)

• Dementia by DSM-III-R/V criteria
• Deficits in two or more areas of cognition
• Progressive worsening of memory and cognitive dysfunction
• Onset age 40-90
• Absence of other systemic/brain disorders
AD Research: Diagnosing AD

Physicians today use a number of tools to diagnose AD:

• a detailed patient history
• information from family and friends
• physical and neurological exams and lab tests
• neuropsychological tests
• imaging tools such as CT scan, or magnetic resonance imaging (MRI). PET scans are used primarily for research purposes
10 warning signs of Alzheimer's

1. Memory loss.
2. Difficulty performing familiar tasks.
3. Problems with language.
4. Disorientation to time and place.
5. Poor or decreased judgment.
6. Problems with abstract thinking.
7. Misplacing things.
8. Changes in mood or behavior.
10. Loss of initiative.
**MMSE**

- Developed for assessment of medical delirium
- Total score is essentially meaningless
- Cognitive domain involvement is key
- Nonetheless, a useful tool given its clinical recognition

**Mini-Mental Status Exam**

1. What is today’s Date? (Month, Date, Year)  
   What is the Day of the Week?  
   What Season of the Year are we in?  
   (Score one point each for correct month, date, year  
   day of the week and season, to a total of 5 points)

2. Can you tell me your address?  
   What town do you live in?  
   What county are we in?  
   What state are we in?  
   (Score one point each for address number, street  
   town, county and state to a total of 5 points)

3. Name three objects (house, bus, dog)  
   Allow one second to say each.  Give one point  
   for each correct answer after the first trial. Repeat  
   up to 6 trials to learn, if not learned by sixth  
   trial, stop)

4. Spell “world” backwards or serial 7’s.  
   (Score one point for each letter in correct order  
   or for each correct subtraction)  
   (Use second line if you do both “world  
   backwards and serial 7’s”)

5. Ask the person to repeat the three objects from  
   Item 3. Score one point for each correct  
   object remembered.

6. Have the person name a pencil and watch  
   (Score one point for each item correctly named.)

7. Repeat the following phrase: “No ifs, ands or buts.”  
   (Score one point if done correctly)

8. Follow a 3-stage command: “Take paper in  
   right hand, fold in half and place on floor.”  
   (Score one point if command is followed)

9. Read and obey the following: “Close Your Eyes.”  
   (Score one point if done correctly)

10. Write a sentence  
    (Score one point for a complete sentence)

11. Copy the Interlocking Pentagons  
    (Score one point if done correctly)

Total Score  
0 - 30 possible if only one of Item 4 used,  
0-35 if both of Item 4 used
MMSE Scores Correlate With Functional Ability

Psychiatric symptoms are prevalent even in early AD
Safety issues in early AD

1. Medications
2. Driving
3. Cooking
Visual rating may be better than volumetric analysis

AD and the Brain

Pet Scan of Normal Brain

Pet Scan of Alzheimer’s Disease Brain
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Alzheimer’s disease pathology
NFTs

Amyloid plaques

Increasing severity of disease
1) APP is a membrane-bound glycoprotein that may serve as a growth factor in injury and repair

2) APP is normally cleaved by $\alpha$-secretase and $\beta$-secretase, but in AD, $\gamma$-secretase is active

3) $\beta$-amyloid is toxic to cells and accumulates in brain tissue as amyloid plaques, a hallmark of the disease
The role of the microtubule-associated protein tau in AD
Neurofibrillary tangles (NFT) & paired helical filaments (PHF)
Cholinergic pathways

Cholinergic Pathways

- Dorsal tegmental pathway
- Projections of the Nucleus Basalis

Adapted from reference 1.

Increasing severity of disease
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The two main types of AD are early-onset and late-onset:

- Early-onset AD is rare, usually affecting people aged 30 to 60 and usually running in families. Researchers have identified mutations in three genes that cause early-onset AD.
- Late-onset AD is more common. It usually affects people over age 65. Researchers have identified a gene that produces a protein called apolipoprotein E (ApoE). Scientists believe this protein is involved in the formation of beta-amyloid plaques.
Alzheimer’s Disease Genetics

Causative (autosomal dominant)

- Chromosome 21 - amyloid precursor protein
- Chromosome 14 - presenilin 1
- Chromosome 1 - presenilin 2

*All mutations increase production of the β-amylloid (Aβ42) peptide*
ApoE not recommended as screening measure

<table>
<thead>
<tr>
<th></th>
<th>POPULATION</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>E2</td>
<td>6%</td>
<td>E2 4%</td>
</tr>
<tr>
<td>E3</td>
<td>81%</td>
<td>E3 56%</td>
</tr>
<tr>
<td>E4</td>
<td>13%</td>
<td>E4 39%</td>
</tr>
</tbody>
</table>

Gomez-Isla et al., 1996 Arch Neurol 39:62-70
Sorl 1 linked to increased risk for sporadic AD

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Alzheimer’s Disease Course, Treatment, and Prevention

Intervention:
- Primary Prevention
- Secondary Prevention
- Treatment

Clinical State:
- Normal
- Pre-symptomatic AD
- Mild Cognitive Impairment
- AD

Brain Pathologic State:
- No Disease
- Early Brain Changes
- AD Brain Changes
- Moderate to Severe Impairment

Disease Progression

National Institute on Aging, USA.
AD Research: the Search for Causes

Epidemiologic Studies

Scientists examine characteristics, lifestyles, and disease rates of groups of people to gather clues about possible causes of AD. The NIA is currently funding epidemiologic studies in a variety of different groups. Two of the studies focus on religious communities. Researchers conduct yearly exams of physical and mental status, and studies of donated brains at autopsy. Some early results indicate:

- Mentally stimulating activity protects the brain in some ways.
- In early life, higher skills in grammar and density of ideas are associated with protection against AD in late life.
<table>
<thead>
<tr>
<th>Study</th>
<th>Agent</th>
<th>Enrollment criteria</th>
<th>Number enrolled or to be enrolled</th>
<th>Planned duration</th>
<th>Currently active</th>
<th>Outcome measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAPT</td>
<td>Naproxen, celecoxib</td>
<td>Cognitively screened, ≥ age 70, first-degree relatives with AD</td>
<td>2,496 enrolled</td>
<td>7–10 years</td>
<td>Treatment stopped</td>
<td>Conversion to dementia and cognitive decline</td>
<td>Not yet available</td>
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<tr>
<td>GEM</td>
<td>Ginkgo biloba extract</td>
<td>Asymptomatic = age 75</td>
<td>5,000</td>
<td>5–7 years</td>
<td>Active</td>
<td>Incident dementia or cognitive tests</td>
<td>Not yet available</td>
</tr>
<tr>
<td>HERS</td>
<td>Estrogen and medroxyprogesterone</td>
<td>Asymptomatic women, mean age 67</td>
<td>1,063</td>
<td>4.2 years</td>
<td>Completed</td>
<td>Cognitive tests (add-on)</td>
<td>One test improved</td>
</tr>
<tr>
<td>Heart</td>
<td>Vitamins E, C, and beta-carotene</td>
<td>Asymptomatic with cardiovascular risk factors, age 40–80</td>
<td>20,536</td>
<td>5 years</td>
<td>Completed</td>
<td>TICS and incident dementia (add-on)</td>
<td>No difference between treated and untreated arms</td>
</tr>
<tr>
<td>Protection</td>
<td></td>
<td></td>
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<tr>
<td>PREADVISE</td>
<td>Selenium, vitamin E</td>
<td>Asymptomatic men, ≥ age 60</td>
<td>10,400</td>
<td>12 years</td>
<td>Completed</td>
<td>Incident dementia and cognitive tests (add-on)</td>
<td>Not yet available</td>
</tr>
<tr>
<td>WHI-PERT</td>
<td>Estrogen and medroxyprogesterone</td>
<td>Women without dementia, ages 65–80</td>
<td>4,532</td>
<td>4 years</td>
<td>Completed</td>
<td>Incident dementia, MCI and 3MS scores</td>
<td>Treated subjects had elevated risk of dementia and worse 3MS scores</td>
</tr>
<tr>
<td>WHI-ERT</td>
<td>Estrogen</td>
<td>Women without dementia, ages 65–80</td>
<td>2,497</td>
<td>5 years</td>
<td>Completed</td>
<td>Incident dementia, MCI and 3MS scores</td>
<td>Treatment group had elevated risk of composite MCI/dementia and worse 3MS scores</td>
</tr>
<tr>
<td>Heart</td>
<td>Simvastatin</td>
<td>Asymptomatic with cardiovascular risk factors, age 40–80</td>
<td>20,536</td>
<td>5 years</td>
<td>Completed</td>
<td>TICS at last visit (add-on)</td>
<td>No difference between treatment groups</td>
</tr>
<tr>
<td>Protection</td>
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<tr>
<td>Study</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>GUIDAGE</td>
<td>Ginkgo biloba extract</td>
<td>Subjective memory complaints, &gt; age 70</td>
<td>2,600</td>
<td>4 years</td>
<td>Ongoing</td>
<td>Incident dementia</td>
<td>Not yet available</td>
</tr>
<tr>
<td>PHS-II</td>
<td>Vitamin E, folic acid, beta-carotene</td>
<td>Asymptomatic, &gt; age 65</td>
<td>10,000</td>
<td>9 years</td>
<td>Ongoing</td>
<td>Telephone cognitive testing</td>
<td>Not yet available</td>
</tr>
</tbody>
</table>

Modified from Sano, with permission.
Hormonal therapy protective?

WHIMS: hormone replacement increases risk of dementia

NSAID use lowers risk of AD

| Table 1: Epidemiological studies of NSAIDs and AD (NA means not applicable) |
|---------------------------------|--------------|---------------|-----------------|-----------------|-----------------|
| Study                          | Diagnosis    | Duration NSAID use | Overall cohort  | AD cases | Relative risk | 95% CI          |
| Incidence                      |              |                |                 |          |                |                 |
| in’t Veld et al. [21]          | AD           | >2 years        | 6989            | 4        | 0.20           | 0.05–0.83       |
|                                | AD           | 1–23 months     | 6989            | 210      | 0.83           | 0.62–1.11       |
|                                | AD           | <1 month        | 6989            | 88       | 0.95           | 0.70–1.29       |
| Stewart et al. [56]            | AD           | >2 years        | 1686            | 81       | 0.65           | 0.33–1.29       |
|                                | AD           | <2 years        | 1686            | 104      | 0.45           | 0.17–0.79       |
| Zandi et al. [70]              | AD           | >2 years        | 3224            | 152      | 0.65           | 0.44–0.95       |
| Lindsay et al. [33]            | AD           | Not given       | 3238            | 53       | 0.98           | 0.23–4.16       |
| Fournier et al. [13]           | Dementia     | >1 year         | 1252            | 50       | 0.50           | 0.10–2.23       |
|                                |              | 50 dizygotic twins | 176            | 25       | 0.19           | 0.06–0.64       |
| Case control                   |              |                |                 |          |                |                 |
| Breitner et al. [6]            | AD           | >1 year         | 50 dizygotic twins | 0.50     | 0.10–2.23       | 0.06–0.64       |
| Breitner et al. [7]            | AD           | >1 year         | 176             | 25       | 0.19           | 0.06–0.64       |
| Yip et al. [69]                | AD           | >6 months       | 1034            | 61       | 0.64           | 0.24–0.98       |
| Beard et al. [5]               | AD           | >7 days         | 285             | 146      | 0.79           | 0.45–1.38       |
| Wolfson et al. [65]            | AD           | Not given       | 599             | 36       | 0.70           | 0.35–1.41       |
| Canadian Health [3]            | AD           | Not given       | 734             | 205      | 0.55           | 0.37–0.82       |
| Population based prevalence    |              |                |                 |          |                |                 |
| Landi et al. [29]              | AD           | Not given       | 2708            | 269      | 0.43           | 0.23–0.82       |
| Anthony et al. [4]             | AD           | Not given       | 4626            | 201      | 0.43           | 0.23–0.75       |
| Broe et al. [8]                | AD           | Not given       | 451             | 78       | 1.40           | Not given       |
| Cognitive decline              |              |                |                 |          |                |                 |
| Hee and Grodstain [15]         | Cognitive decline | 8 years          | 16128          | NA       | 0.79           | 0.62–1.02       |
| Rozzini et al. [51]            | Cognitive decline | >3 years, 0.82 | 7671, 0.69–0.98 | NA       | No significant effect |
| May et al. [35]                | Cognitive decline | 3 years          | 1310           | NA       | No significant effect |
| Henderson et al. [16]          | Cognitive decline | 3.6 years aspirin | 588           | NA       | No significant effect |
| Saag et al. [52]               | Cognitive decline | >2 weeks         | 2087           | NA       | Word recall decline |
| Hanlon et al. [14]             | Cognitive decline | Not given        | 2765           | NA       | No significant effect |
| Nilsson et al. [45]            | Cognitive decline | >3 years aspirin | 702            | NA       | 0.41           | 0.26–0.67       |
| Jonker et al. [24]             | Cognitive decline | 3 years aspirin | 612            | NA       | 0.30           | 0.09–0.82       |
| Sturmer et al. [57]            | Cognitive decline | 3 years aspirin | 3793           | NA       | No significant effect |
ADAPT: NSAIDs do not reduce the risk of developing AD

- 2,528 subjects
- 4 year duration
- NSAIDs actually increased the risk of developing AD

Drugs used to treat mild to moderate AD symptoms include:

- Aricept (donepezil)
- Exelon (rivastigmine)
- Razadyne (galantamine)
- Namenda (memantine)
- These drugs can help improve some patients’ abilities to carry out activities up to a year or so, but they do not stop or reverse AD.

Scientists are also studying agents that someday may be useful in preventing AD. For example, they have experimented with a vaccine against AD. Although the first clinical trial was stopped due to side effects in some participants, valuable information was gathered.
Treatment is Important: Delaying dementia onset can significantly decrease the prevalence of disease.

Cholinergic Synaptic Transmission

ChE inhibitors reduce ACh hydrolysis in remaining neurons and may increase cholinergic neurotransmission.
Long-term Effects of Donepezil on Cognition: ADAS-Cog Mean Change From Baseline

- Decline in ADAS-Cog score based on the natural history of untreated patients with moderate Alzheimer’s disease*

Change in NPI over 12 weeks treatment with donepezil

Normal function

Alzheimer’s disease

Treated with Memantine
Increased benefit in mod-severe AD adding memantine to AchEI

This is Alzheimer’s disease untreated
Let’s add a cholinesterase inhibitor...

Minimal improvement seen in most cases

In several years do you want to be here?

Or here?
Now let’s add a NMDA antagonist to our cholinesterase inhibitor...

In several years do you want to be here?

Level of detection

100%
Researchers also are looking at other treatments, including:

- cholesterol-lowering drugs called statins
- anti-oxidants (vitamins) and folic acid
- anti-inflammatory drugs
- substances that prevent formation of beta-amyloid plaques
- nerve growth factor to keep neurons healthy
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- Non-AD Dementias: VaD, DLB, FTD
It’s clear that dementia is a “mixed bag” of disorders.
Alzheimer’s disease

Vascular dementia

Dementia with Lewy bodies

Frontotemporal dementia
Alzheimer's disease
Vascular dementia

Dementia with Lewy bodies
Frontotemporal dementia

Production of Amyloid Plaques

Unaffected Microtubules
Alzheimer's Disease Microtubules
Alzheimer’s disease (NINDS-ADRDA)
- Dementia by DSM-III-R/V criteria
- Deficits in two or more areas of cognition
- Progressive worsening of memory and cognitive dysfunction
- Onset age 40-90
- Absence of other systemic/brain disorders

Vascular dementia (NINDS-AIREN)
- Dementia by DSM-III-R/V criteria
- Cerebrovascular disease present:
  a) focal neurologic signs (stroke)
     • history of stroke not necessary
  b) CT or MRI evidence of stroke
- Onset of dementia within 3 months of stroke, or abrupt deterioration of cognitive function or stepwise course

Dementia with Lewy bodies (3rd Int. Workshop on DLB)
- Dementia by DSM-III-R/V criteria
- Deficits in cognition may not be memory (usually attention/spatial)
- Parkinsonism
- Early hallucinations
- Fluctuations
- Supportive:
  • Depression
  • REM sleep behavior disorder

Frontotemporal dementia (NIH work group on FTD)
- Prominent behavioral disorder
- Loss of interpersonal skills
- Emotional blunting
- Perseveration or impersistence or
- Language involvement
- Comprehension or fluency
- Cognition typically preserved
- Can be assoc with MND/ALS
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Thanks for your attention!

Questions?