Goals for Today

• When is it dementia?
• What treatments are available?
• When should we use which treatments?
• What are the controversies and horizons?
What is Dementia?

- An acquired syndrome of decline in global cognitive functions sufficient to affect daily life in an alert patient.

KEYWORDS

– Acquired
– Decline
– Global
– Affect Daily Life
– Alert patient
Where Do People With Alzheimer’s Disease Live?

Source: Alzheimer’s Association, 2004
CC: Worry about memory in 76 yr old woman

HPI per Pt:
• Difficulty remembering names
• Acutely embarrassing
• Tearful while telling story

Other relevant history:
• No head trauma
• No tremor, gait or incontinence problems
• No psychotic sx
• No wandering, lost

HPI per Dtr:
• Onset 18 mo prior with insistence knew a new acquaintance
• Errors in names and details of close relatives
• Difficulty writing checks
• Tea kettle burned dry
• Indep all ADLs
• Well groomed but more stains on clothing
Case 1: Worry about memory in 76 yr old woman

Educ: BS degree and taught 3rd grade.
FH: 1 aunt late onset dementia
PMH:
• HTN
• Macular degeneration
• GERD
Meds:
• lisinopril
• prilosec

Exam:
BP 132/60
Neuro NL.
Speech Fluent without word finding difficulties.
MMSE 26/30 using serial 7s. 28/30 using WORLD.
Clock-drawing Placement of 11:20 excellent.
Affect Worried and fretful.
What is the diagnosis?

A. Depression
B. Dementia
C. Anxiety
D. Dementia + affective disorder
When is it dementia?

• Approach to Diagnosis
  – Pretest probability
  – Testing to adjust probabilities -MMSE
  – Consider alternative diagnoses
What is the pretest probability of having dementia?
### MMSE Test Performance

Standard Used – NINCDS-ADRD Criteria

<table>
<thead>
<tr>
<th>MMSE</th>
<th>LR+</th>
<th>Pre-test Probability of Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2%</td>
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<tr>
<td></td>
<td></td>
<td>2%</td>
</tr>
<tr>
<td>27</td>
<td>3.2</td>
<td>6</td>
</tr>
<tr>
<td>26</td>
<td>4.4</td>
<td>8</td>
</tr>
<tr>
<td>25</td>
<td>6.3</td>
<td>11</td>
</tr>
<tr>
<td>24</td>
<td>8.5</td>
<td>15</td>
</tr>
<tr>
<td>23</td>
<td>10.4</td>
<td>17</td>
</tr>
<tr>
<td>22</td>
<td>12.5</td>
<td>20</td>
</tr>
<tr>
<td>21</td>
<td>14.2</td>
<td>22</td>
</tr>
<tr>
<td>20</td>
<td>17.0</td>
<td>26</td>
</tr>
<tr>
<td>19</td>
<td>21.3</td>
<td>30</td>
</tr>
<tr>
<td>18</td>
<td>20.0</td>
<td>29</td>
</tr>
<tr>
<td>17</td>
<td>27.5</td>
<td>36</td>
</tr>
<tr>
<td>16</td>
<td>49.0</td>
<td>50</td>
</tr>
</tbody>
</table>

Merian, Arch Neur 53(10) 1043-1054
Consider Alternative Diagnoses?

• Depression
• Delirium
• Mild Cognitive Impairment
• Benign senescent changes of aging
Dementia Vs. Depression

- Dementia
  - Insidious onset
  - Long duration
  - No psychiatric history
  - Near-miss answers
  - Stable cognitive loss
  - Memory loss greatest for recent events

- Depression
  - Abrupt onset
  - Short duration
  - Prior psychiatric history
  - Doesn’t know answers
  - Fluctuating cognitive loss
  - Memory loss for recent and remote events
  - Maintain language and motor skills
If Dementia – Which type?
Differential Diagnosis for Dementia

• Alzheimer’s disease 60-70%
• Vascular dementia 10-15%
• Dementia with Lewy Bodies 5-10%
• Lobar degenerations 5-8%
  – Frontotemporal dementia (Pick’s)
• Mixed 10-15%
• Other 2-5%
DSM-IV Diagnostic Criteria for Alzheimer’s Disease

- Development of cognitive deficits manifested by both
  - impaired memory
  - aphasia, apraxia, agnosia, disturbed executive function
- Significantly impaired social, occupational function
- Gradual onset, continuing decline
- Not due to other CNS or physical conditions (e.g., Parkinson’s Disease, delirium)
- Not due to an Axis I disorder (e.g., schizophrenia)
THE 4 A's OF ALZHEIMER DISEASE

<table>
<thead>
<tr>
<th></th>
<th>IMPAIRMENT IN</th>
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<tbody>
<tr>
<td>AMNESIA</td>
<td>memory</td>
</tr>
<tr>
<td>APHASIA</td>
<td>language</td>
</tr>
<tr>
<td>APRAXIA</td>
<td>doing</td>
</tr>
<tr>
<td>AGNOSIA</td>
<td>recognition/perception</td>
</tr>
</tbody>
</table>

After McHugh and Folstein
Are there Reversible Dementias?

Dementia in Elderly Outpatients: A Prospective Study.

- Objective: Prospective study to determine outcomes with a standard approach to evaluation of outpts with global mental impairment
- N=107
- H&P, basic labs, CT head, CXR, EKG
- Follow up at least 6 mo, most 2 years
Identified Potentially Reversible Diagnoses

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Patients (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroidism or myxedema</td>
<td>4</td>
</tr>
<tr>
<td>Subdural hematoma</td>
<td>2</td>
</tr>
<tr>
<td>Transient ischemic attacks</td>
<td>1</td>
</tr>
<tr>
<td>Rheumatoid vasculitis</td>
<td>1</td>
</tr>
<tr>
<td>Manic-depressive illness</td>
<td>1</td>
</tr>
<tr>
<td>Medication side effect</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>3</td>
</tr>
<tr>
<td>Multiple</td>
<td>3</td>
</tr>
</tbody>
</table>

Outcomes:
Returned to Normal – Only 3
Progressive Cognitive Decline – 8/13 (with data at 2 yrs)

Case 1: Worry about memory in 76 yr old woman

76 yr old woman presents to the clinic worried about her memory. She is accompanied by her daughter. The patient relates that she has difficulty remembering names. This is acutely embarrassing and she becomes tearful when telling her story and clearly has a great deal of anxiety.

After hearing the patient’s story, the daughter contributes her observations. The first sign of difficulty was 18 mo prior. Pt was insistent that she knew a person previously when they had just met on vacation. Since then there have been more issues around errors related to names of close relatives and difficulty writing checks. Husband now does the finances. She reveals that 1 yr ago, they took away the tea kettle after it repeatedly boiled dry. They changed to an electric kettle but once this winter she put it on the burner and turned it on. It was discovered because of the smell by the daughter.

The patient does all her own ADLs and is generally well groomed although stains on clothes noted more now. She has not gotten lost.

PMH is significant for HTN, macular degeneration and GERD. Med are prilosec, lisinopril. SH – She has a B.S. degree and is a retired 3 grade teacher. She lives with her husband and has several daughters. FH – Parents lived to age of risk without memory impairment or strokes. One aunt with late onset dementia.

BP 132/60  Neuro exam nL. Speech fluent without word finding difficulties. MMSE 26/30 using serial 7s. 28/30 using WORLD. Clock-drawing with placement of 11:20 excellent. Affect worried and fretful.
What is the diagnosis?

A. Depression
B. Dementia
C. Anxiety
D. Dementia + affective disorder
What treatments are available?

- And how do we know if they work?
- We will explore this through cases
Case 2: A story

You are the physician for a husband and wife.

- He is 78 with AD. Recently in hosp for delirium, BOO and had foley placed
- Hospital f/u wife reports he swatted at her.
- VNA reports pt pulls it out & not going back in
- Develops overflow incontinence
- Month later wife in ED with CP, BP200/100 on 4 meds, refuses admission
- Later still wife faints in shower after waking in soaked bed from husband’s incontinence
What would be meaningful outcomes that would help this patient?

A. Cure/Delay Disease Onset
B. Slow progression or palliate symptoms
C. Reduce economic costs
D. Caregiver health
E. Prevent institutionalization

How you would measure these outcomes in an intervention trial?
Interventions We Will Examine

• Spouse-Caregiver Intervention
• Cholinesterase Inhibitors
• NMDA antagonist
• Vit E and selegiline
A Family Intervention to Delay Nursing Home Placement of Patients with Alzheimer’s Disease: A RCT

Mittelman MS et al. JAMA 1996;276:1725.

Sample: Referred, volunteer 206 spouse-caregivers of AD pts living at home with > 1 relative in area

Intervention enrolled over 3.5 yrs:
1. Indiv. & Family counseling: task oriented, teaching techniques for problem solving, improve communication and support of primary caregiver
2. Caregivers joined a support group (any)
3. 24 hr available counselor for crises or questions

F/u up to 8 years

Funding: NIMH
## Results - Mittelman

<table>
<thead>
<tr>
<th>Caregiver Sex</th>
<th>Treatment Group</th>
<th>Control Group</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median Time ±SE, d</td>
<td>95% CI</td>
<td>Median Time ±SE, d</td>
</tr>
<tr>
<td>Total (unadjusted for sex)</td>
<td>1356±288</td>
<td>791 to 1921</td>
<td>905±178</td>
</tr>
<tr>
<td>Female</td>
<td>1021±113</td>
<td>799 to 1243</td>
<td>777±126</td>
</tr>
<tr>
<td>Male</td>
<td>1680±247</td>
<td>1195 to 2165</td>
<td>1129±118</td>
</tr>
<tr>
<td>Total (adjusted for sex)†</td>
<td>1203±107</td>
<td>944 to 1412</td>
<td>874±97</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval.
†This row represents a weighted average of sex-specific medians or differences in medians. The weights are 0.723 for female and 0.277 for male caregivers. These weights are inversely proportional to the estimated variance of the sex-specific difference between medians in the final column.
Survival Curves for Time to Nursing Home Placement

Cumulative Proportion of Patients

From Baseline

Years

Remaining out of a nursing home

How would we implement the intervention?

- No one pays for this type of intervention
- Direct to the Alzheimer’s Disease Assoc.
  - Information (www.alz.org)
  - Possibly eligible for respite
  - 24 hr question phone line 800-272-3900
- Know community resources and contacts
- Anticipatory guidance – improve our knowledge
- Medicaid eligible pts may have options
Case 3: Unfolding Symptoms in 89 yo man

**Time 0** – He has no complaints but wife discreetly comments that he seems less sharp. Retired PhD literature. Continues to write academic works.

**Time 4 mo** – He now admits memory issues but feels “no worse than anyone else his age”. Not cut down on alcohol. Testing is unchanged.

**Time 8 mo** - When alone in room, he admits to short-term memory problems. Wife adds that if given several instructions he will only do one. He is still reading but rereading the same book over & over. The children are now concerned about his behavior. Supermarket fluency 5. Trails B scores 20th percentile.
What do we make of normal MMSE?

If they wanted a medication, which would you recommend in addition to getting off alcohol?

A. Sertraline (Zoloft)
B. Donepezil (Aricept)
C. Disulfiram (Antabuse)
D. Memantine (Namenda)
E. None of the above
Cholinesterase Inhibitors

- Tacrine (Cognex) – Not available
- Donepezil (Aricept) - QD
- Galantamine (Reminyl) - BID
- Rivastigmine (Exelon) – BID

- Major ADR – GI side effects
Rice Testimony:
Question of Tone
The White House is still deciding what tone Condoleezza Rice should strike when she testifies before the Sept. 11 commission tomorrow, officials involved in the internal debate said.

Ms. Rice and her colleagues have prepared an opening statement that one official described as almost a day-by-day overview of what the administration was doing in the months before the attacks.

The statement also seeks to counter the contention of the panel’s leaders, Thomas H. Kean and Lee H. Hamilton, that the attacks were probably preventable, based on the intelligence available in the summer of 2001.

Ms. Rice has ruled out issuing the kind of apology made by her former counterterrorism chief, Richard A. Clarke, who said two weeks ago that the government had failed the country and that he had as well.

Article, Page A13.

Nominal Benefit is Seen in Drugs for Alzheimer’s
Continuing Use Debated
Prospects for Developing Better Treatments Soon Are Called Unlikely

By DENISE GRADY
The drugs now available to treat the memory and thinking problems of Alzheimer’s disease have not lived up to the public’s high expectations for them and offer such modest benefits on average that many doctors are unsure whether to prescribe them.

Although the drugs have their advocates, grateful for any sign of improvement, others express disappointment in light of earlier hopes that the drugs approved in the last decade would stop the disease or markedly slow it.

At a recent meeting at Johns Hopkins University, doctors and other health professionals heard Alzheimer’s researchers debate the usefulness of the drugs and the prospects of better treatments becoming available any time soon. Some researchers say it may be decades before real progress is made in reducing the toll.

Up to 12 Marines Die in Raid on 1 As Fierce Fighting Spreads to 6

An American marine loaded onto a truck a body bag that held a comrades war remains. By DENISE GRADY

Maurizio Gambarini/European Pressphoto Agency

Data Churners
Try to Pinpoint Voters’ Politics

“...
Controversy

• Many drug trials have serious problems
  – Highly selected study subjects
  – Often extensions of short RCT
  – Use measures with unclear clinical relevance
  – High drop rates without Intention to treat analysis or drop-out retrieval
  – Drug company funding
Long-term donepezil treatment in 565 patients with Alzheimer’s Disease (AD2000): RCT.

Sample: Referred for memory clinic. There must be uncertainty whether pt would benefit. No exclusions other than contraindication to med. Had a caregiver.

Design: Double-blind RCT with a 12 wk run in period. Sub-randomization to 5mg or 10 mg. ITT analysis with retrieved drop-outs. Pts met DMS IV criteria for AD with or without coexisting vascular dementia. Had 48 wk intervention followed by 4 wk washout then 48wk intervention etc.

Measures: Primary- institutional care or loss of 2/4 ADLs or 6/11 IADLs. Secondary- all the usual scales

Funding: NHS Executive R&D. Drug companies sold them the drug but had no other involvement.
Primary Outcome Measures
AD2000

Entry into institution

Entry into institution or loss fcn
Secondary Outcome Measures

Change in MMSE

- Donepezil: Mean 0.93 (SD 3.24)
- Placebo: Mean 0.00 (SD 2.96)

Change in BADLs

- Treatment effect 1.02 (SE 0.28) p<0.0001

What would be a clinically significant change in score?
- MMSE avg. decline in AD 3 pt/yr
- BADLs 3 points
Secondary Outcome Measures

Caregiver health

Active caregiver time

Neuropsychiatric symptoms
ADAS-Cog on Donepezil

Change Score

ADAS-Cog

Weeks in Trial

Clinical Improvement

Clinical Decline

10 mg/d

5 mg/d

Placebo

Rogers SL et al. 1996.
JB’s remake of previous slide

ADAS-Cog on Donepezil

Change in ADAS-Cog

Weeks

- Placebo
- 5mg
- 10mg
JB’s remake of previous slide on 70 pt scale of the ADAS-Cog

ADAS-Cog on Donepezil (hypothetical)
Case 4: Where’s the door?

You are the physician at a nursing home and asked to assess one of your patients for increased agitation. Specifically, the patient is pacing and going into other patient’s rooms. He is less redirectable and will resist care and rarely strike out at the nurse’s aides.

Evaluation reveals no acute medical process or apparent pain and no new medications have been added. He is on donepezil.
Aside from creating a safe environment that allows pacing, what medications would you add?

A. Lorazepam (Ativan)
B. Risperidone (Risperidal)
C. Olanzapine (Zyprexa)
D. Memantine (Namenda)
E. None of the above
Memantine Treatment in Patients with Moderate to Severe Alzheimer’s Disease Already Receiving Donepezil.

Sample: NINCD-ADRD probable AD. MMSE of 5-14, community dwelling, ambulatory, and had caregiver. Excluded if any of multiple active medical conditions, any evidence of any other CNS disease.

Design: 24 wk double blind RCT. Modified ITT analysis but not all pts accounted for.

Measures: Primary – Severe Impairment Battery and ADCS-ADL
Secondary – CIBIC-Plus, NPI, BGP, FAST

Length of f/u: 24 wks

Funding: Forest Research Institute (company that makes memantine) and also gave statistical and editorial support. Several authors are employees of company with stock options.
Memantine: Methods

DB-PC-RCT
- 404 pt randomized
- 200 each arm
- not all participants in final analysis
- Sample healthy without comorbidity or other neurologic process

SIB and ADCS-ADL19 by Visit (Observed Case) and at End Point (LOCF)

SIB has 100pt scale

Distribution of CIBIC-Plus Ratings at End Point (LOCF)

Memantine:
No statistically significant ADRs in the drug trials

Table 3. Adverse Events Reported in at Least 5% of Patients in Either Treatment Group

<table>
<thead>
<tr>
<th>Adverse Event, No. (%)</th>
<th>Placebo (n = 201)</th>
<th>Memantine (n = 202)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitation</td>
<td>24 (11.9)</td>
<td>19 (9.4)</td>
</tr>
<tr>
<td>Confusion</td>
<td>4 (2.0)</td>
<td>16 (7.9)</td>
</tr>
<tr>
<td>Fall</td>
<td>14 (7.0)</td>
<td>15 (7.4)</td>
</tr>
<tr>
<td>Influenza-like symptoms</td>
<td>13 (6.5)</td>
<td>15 (7.4)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>16 (8.0)</td>
<td>14 (6.9)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (2.5)</td>
<td>13 (6.4)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>10 (5.0)</td>
<td>12 (5.9)</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>6 (3.0)</td>
<td>11 (5.4)</td>
</tr>
<tr>
<td>Accidental injury</td>
<td>16 (8.0)</td>
<td>10 (5.0)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>13 (6.5)</td>
<td>10 (5.0)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>8 (4.0)</td>
<td>10 (5.0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17 (8.5)</td>
<td>9 (4.5)</td>
</tr>
<tr>
<td>Fecal incontinence</td>
<td>10 (5.0)</td>
<td>4 (2.0)</td>
</tr>
</tbody>
</table>

*Patients may have reported more than 1 adverse event.
Vitamin E and AD (cont.)

Event-free survival (%)

Days

Baseline score on MMSE included as a covariate

Vit E Trial Comments

- No benefit seen in cognitive or functional measures
- Findings yet to be duplicated
- ADRs related to selegiline such that no one uses it
When to use which treatment?

- Spouse-Caregiver Intervention
  - Always
- Acetyl cholinesterase inhibitors
  - FDA indicated for mild to mod AD
- NMDA inhibitor
  - FDA indicated for mod to sev AD
- Vit E
  - Many dementia doctors use it
Alzheimer’s Disease Progression

- Early diagnosis
- Mild-moderate
- Severe

- Cognitive symptoms
- Loss of Functional Abilities
- Behavioral problems
- Nursing home placement
- Death

Years: 0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8 8.5 9

MMSE Score: 0 5 10 15 20 25 30

“The indication for treatment of severe dementia raises ethical issues. The benefit of slowing AD progression in the later stages can be controversial. It is possible that the drug only extends the total time of deterioration without reducing personal or social burden of the disease. Therefore it is important to include measures of patient quality of life, caregiver burden and costs among outcome variables.”

Areosa SA. Cochrane Review 2003(1):CD003154
What’s on the horizon?

• Prevention trials
  – Statins
  – NSAIDS
  – Hormones
  – Anti-oxidants

• Mild Cognitive Impairment trials

• Treatment trials
  – Vaccines
  – Beta amyloid blockers
  – Nerve growth factors
• Evaluate & document the mental status and follow over time

• Support the caregiver
  – How to pay for social and support interventions?
  – Know your resources
  – 24 hr help line AD Assoc. 800-272-3900

• Consider ChI and NMDA as potential palliative treatments