Alzheimer's Disease (AD): A National Health Problem

• Alzheimer's Disease (AD) is a neurodegenerative brain disorder that afflicts approximately 500,000 people aged 80+ each year in the US
• Over 4 million adult Americans now have AD
• AD is the most common cause of dementia in the elderly
• Incorrect diagnosis ranges from 15%-40%
• There will be at least 7 million patients with AD in the US by the 21st century

The Amyloid Hypothesis

• Amyloid deposits
  - Correlates with AD pathology and reduced cognitive function
  - Accumulate with advancing age
  - Accumulate in neuritic plaques over span of 30 years
  - Composed of \( \beta \)-A4 protein

ApoE

• Apolipoprotein (ApoE) cholesterol transporter
• 3 alleles (gene forms):
  - E2
  - E3
  - E4
• One form inherited from each parent
• E4 form as significant Alzheimer risk factor

Genetic Research

• Research has produced evidence of a link between AD and chromosomes 1, 14, 19, and 21
• Chromosomes 1, 14, and 21 have been linked with early-onset AD, an extremely rare form of the disease
• ApoE4 gene located on chromosome 10 has been associated with late-onset AD, the most common form of the disease

Alzheimer's Disease (AD): Classified by Age and Gender

<table>
<thead>
<tr>
<th>Age Group (yr)</th>
<th>Males (%)*</th>
<th>Females (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>65-69</td>
<td>0.37</td>
<td>0.20</td>
</tr>
<tr>
<td>70-74</td>
<td>0.70</td>
<td>1.16</td>
</tr>
<tr>
<td>75-79</td>
<td>1.37</td>
<td>1.16</td>
</tr>
<tr>
<td>≥ 80</td>
<td>3.00</td>
<td>2.25†</td>
</tr>
</tbody>
</table>

*Midrange
†Hay JW, Ernst RL. Am J Public Health. 1987; 77: 1169-1175

Dementia and Alzheimer's Disease

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Selected NINCDS-ADRDA Criteria

- **Possible AD**
  - dementia syndrome in the absence of neurologic, psychiatric, and systemic disorders sufficient to cause dementia
- **Uncertain/unlikely AD**
  - sudden onset
  - focal neurologic findings
  - early seizures or gait disturbances


Selected NINCDS-ADRDA Criteria

- **Probable AD**
  - dementia
  - deficits in two or more cognitive areas
  - progressive worsening of memory and other cognitive functions
  - no disturbances of consciousness


Differential Diagnosis

- Causes of dementia can include:
  - vascular disease
    - multi-infarct dementia
    - Parkinson’s disease
    - Pick’s disease
    - Huntington’s disease
    - normal pressure hydrocephalus
  - metabolic disorders
    - vitamin B₁₂ deficiency
    - chronic drug intoxication
    - hypothyroidism
    - alcoholism
  - infectious causes
  - HIV
  - neurosyphilis
    - bacterial meningitis
    - major depression

The clinical diagnosis of AD can be made with 85% - 90% accuracy

Vascular Dementia/ Multi-Infarct Dementia (MID)

- By definition, dementia due to vascular disease
- Clinically, different varieties
  - multiple large infarcts
    - large vessel disease
  - lacunar state
  - leukoaraiosis
    - multiple tiny white matter lesions
  - collagen vascular disease

Lewy Body Disease

- Clinically resembles combination of Parkinson’s and AD
- Pathologically diffuse Lewy Bodies and Alzheimer’s pathology
  - especially “plaque – only”
- May respond to medications

Lewy Body Disease

- Probably 3rd most common cause of dementia, after AD and MID
- Psychological symptoms include:
  - fluctuations
  - psychosis
  - increased sensitivity to antipsychotics
- Two of these make diagnosis likely:
  - fluctuating cognition
  - visual hallucinations
  - parkinsonism without tremor
Prion Disease

AD: Stage I
- Memory loss
  - mainly recent events
- Some judgmental deficits
- Able to do ADL
- Some word finding trouble
- Subtle personality changes

AD: Stage II
- Period of apraxia and agnosia
- Begins to lose ability to do things
  - first, complex acts
  - later, elementary
- Trouble recognizing meaning, nature, or use of objects
  - later, includes relatives
- Communication skills clearly impaired
- Delusions/hallucinations develop

Apraxia
- Loss of ability to carry out familiar purposeful movements or acts
  - in the absence of paralysis

Agnosia
- Loss of power to recognize the import of sensory stimuli
  - though the sensory organs are intact

Aphasia
- Loss of ability to use language through symbolic means
  - spoken or written words
Symptoms Due to Delusions

- Wandering
- Aggression
- Nocturnal psychosis
- Hoarding and hiding
- Unusual urination/defecation
- Unusual dietary habits

AD: Stage III

- Period of incontinence
- Most ADL skills lost
- Delusions/hallucinations replaced by placidity and amotivation
- Communication slowly lost completely
- Ultimately, totally vegetative

AD: Course

- Progression vs. plateau
- Reversal of childhood development steps

Effective Management of the 3 Domains of AD Symptomology

- Cognition
- Behavior
- ADL

Note: No proportion implied in the pie slides

Driving Difficulties

- Warning signs
  - gets lost easily
  - driving too slowly
  - aggressive driving
- Strategies to prevent driving
  - take away car keys
  - other preventive measures

Fire

- No unsupervised stove use
- Cautious use of microwave
- No kerosene, etc.
Protecting the Wealth

- No independent check writing
- No large sums of cash
- No valuable jewelry
- Power of attorney early

Treatment Strategies

- Transmitter replacement
- Growth factors
- Anti-inflammatory drugs
- Amyloid modifiers
- Other

Action of Acetylcholine

Acetylcholinesterase degrades acetylcholine

Acetylcholinesterase inhibitors block acetylcholinesterase

Activities that Improved Significantly with Rivastigmine Compared with Placebo

<table>
<thead>
<tr>
<th>Item</th>
<th>GDS≤3</th>
<th>GDS=4</th>
<th>GDS≥5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ability to handle money</td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ability to tell time</td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time spent on hobbies</td>
<td>√</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Ability to dress properly</td>
<td>√</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Reduced forgetfulness</td>
<td>√</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Time rearranging objects</td>
<td>√</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Participation in family finances</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ability to use phone</td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confusion in different settings</td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proper eating manners</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Rivastigmine Effect on Cognition in Moderately Severe Patients

ADAS-Cog mean change in patients with GDS ≥5

Tolerability of Rivastigmine: Common (≥ 10%) Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Incidence (%)</th>
<th>Severe (%)</th>
<th>Median duration per episode (days)</th>
<th>Incidence (%)</th>
<th>Severe (%)</th>
<th>Median duration per episode (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>37</td>
<td>2</td>
<td>2</td>
<td>12</td>
<td>&lt;1</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>23</td>
<td>2</td>
<td>1</td>
<td>6</td>
<td>&lt;1</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>19</td>
<td>1</td>
<td>2</td>
<td>11</td>
<td>&lt;1</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16</td>
<td>&lt;1</td>
<td>2</td>
<td>11</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Headache</td>
<td>15</td>
<td>1</td>
<td>2</td>
<td>12</td>
<td>&lt;1</td>
<td>2</td>
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<tr>
<td>Anxiety</td>
<td>13</td>
<td>1</td>
<td>20</td>
<td>3</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>11</td>
<td>1</td>
<td>4</td>
<td>6</td>
<td>&lt;1</td>
<td>2</td>
</tr>
</tbody>
</table>

Data on file: Novartis Pharmaceutical Corp.
Dosing and Administration of Rivastigmine

- Starting dose: 1.5 mg bid for a minimum of 2 weeks
- Dose range: 3 to 6 mg bid (i.e.: 6-12 mg/day)
  - increase the dose after a minimum of 2 weeks of treatment at lower dose
  - the maximum dose is 6 mg bid (12 mg/day)
- Rate of titration should be guided by tolerability
- All doses should be taken with food

Pharmacologic Management

- Other Cholinesterase Inhibitors
  - Donepezil (Aricept)
  - Galantamine (Reminyl)
- A drug with a different action
  - memantine, an NMDA receptor blocker
    - Namenda
- The drugs may be used together

Other Pharmacologic Management Strategies

- Treatment of delusions
- Monitor dosage closely
- “Sleeper” drugs
- Avoid benzos

Non-pharmacologic Management

- AD patients do not tolerate change well
  - hospital
  - holidays
    - any change leads to unwanted behavior
    - warn caregiver
- Eating habits
  - tendency towards sweets
  - use supplements

Non-pharmacologic Management

- See patients at regular intervals
  - every 6 months
  - If not, regular phone conversation with caregivers
- Purpose of treating AD is to keep the patient in the home
  - nursing home costs about $3,000 per month
    - “the pauperizer of the middle class”
- Keep the caregiver happy
  - do proper workup to ensure diagnosis of non-reversible dementia