Alzheimer’s Disease

Andrew Blumenfeld, MD
Neurology
Scripps, San Diego
Alzheimer’s Disease: More Than Memory Loss

- Progressive memory impairment
- Language affected
- Poor visual recognition
- Learnt sequences lost
- Impaired social or occupational function
- Changes in personality, behavior, and judgment

NINCDS-ADRDA Criteria
Making the Diagnosis of Alzheimer’s Disease

- History
- Physical
- Neurologic and Mini–Mental exam
- Blood tests
- Imaging studies: CT, MRI
Symptoms of Alzheimer’s Disease

1. Memory loss affecting skills
2. Difficulty performing familiar tasks
3. Problems with language
4. Disorientation regarding time or place
5. Impaired judgment
6. Problems with abstract thinking
7. Misplacing objects
8. Changes in mood or behavior
9. Changes in personality
10. Loss of initiative
Barriers to Early Detection of Alzheimer’s Disease

- Misidentification by the family of early signs as normal aging process
- Social skills often maintained in early AD
- Denial and lack of insight by patient
- Reluctance to report symptoms — stigma
- Lack of definitive screening tools
Prevalence and Impact of AD

- AD is the most common cause of dementia
- Affects 10% of the population over the age of 65 and 50% over the age of 85
- Approximately 4 million AD patients in the United States
- Annual treatment costs = $100 billion
- AD is the fourth leading cause of death in the United States
- The overwhelming majority of patients live at home and are cared for by family and friends

Differential Diagnosis of Dementia

- Strokes: 18%
- Parkinson's like Lewy body disease: 15%
- AD: 65%

Progress of AD

- Early diagnosis
- Mild-moderate
- Severe

- Cognitive symptoms
- Loss of ADL
- Behavioral problems
- Nursing home placement
- Death

MMSE score

Years

## Patient Functioning as Disease Progresses

### Stages of Alzheimer’s Disease

<table>
<thead>
<tr>
<th>Activities of daily living (ADLs)</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problems with routine tasks</td>
<td></td>
<td>Needs help with basic ADLs (e.g., feeding, dressing, bathing)</td>
<td>Progresses to total dependence on caregiver (e.g., feeding, toileting)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Behavior</th>
<th>Changes in personality</th>
<th>Anxiety, suspicion, pacing, insomnia</th>
<th>Agitation, wandering</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Cognition</th>
<th>Confusion and memory loss</th>
<th>Difficulty recognizing family and friends</th>
<th>Loss of speech Misidentifies or is unable to recognize familiar people</th>
</tr>
</thead>
</table>
Impact of Alzheimer’s Disease on Caregivers

- More than 70% of patients with Alzheimer’s disease live at home, and almost 75% of home care is provided by family and friends
- 46% to 59% of caregivers are depressed, according to various studies
- Caregivers get more medical illnesses than non-caregivers
Alzheimer’s Disease in the Long-Term Care Setting

- Alzheimer’s disease affects a significant population in long-term care facilities
  - 1.5 million people resided in certified nursing facilities from 1999 to 2000
  - Approximately 45% of nursing home residents have AD
Neurofibrillary Tangles and Amyloid Plaques
Brain Scans

- CT/MRI are especially indicated for:
  - Headache
  - Abrupt or rapid onset of cognitive decline
  - Onset of dementia before age 65
  - Gait changes or motor signs
  - Seizures

SPECT and PET

- Cerebral blood flow and glucose metabolism can be measured by single photon emission computed tomography (SPECT) and positron emission tomography (PET)
- SPECT and PET typically show reduced activity in the parietal lobes in AD
Typical AD PET Scan

Provided courtesy of M. Mega, MD, PhD, Department of Neurology, UCLA School of Medicine.
Laboratory Tests

- Complete blood count
- Serum electrolytes (including calcium)
- Liver function tests
- BUN and creatinine
- Thyroid-stimulating hormone
- Serum vitamin B$_{12}$ level
- ESR
- HIV Serology

Tests

• Apolipoprotein E genotyping
  – Not recommended for screening
    • 50% of AD patients do not carry APOE ε4

Possible Risk Factors

- Age
- Family history
- Female gender
- Low testosterone
- Head injury
- Strokes
- Depression
- Elevated plasma homocysteine levels
- APO E genotype and Down’s syndrome
Risk Reduction?

- ? Cholesterol lowering agents
- ? Antioxidants: Vitamin E and C
- ? Anti-inflammatories
- ? Estrogen
- ? Reduce Homocysteine: Folate
- Aspirin
Other Topics

- Advance Directives
- DMV reporting
- Community Social Services
Cholinergic Pathways From the Basal Forebrain

Acetylcholinesterase Inhibition

Donepezil significantly improved cognition versus placebo as measured by MMSE scores in a 1-year, multinational clinical trial.

Data on file. Eisai Inc., Teaneck, NJ.
Treatment benefits were lost when donepezil was discontinued as measured by the decline in ADAS-cog scores in an open-label extension of Study 302.

*Other studies have estimated the decline to range from 6 to 12 points annually.

Metabolism of medications

**CENTRAL NERVOUS SYSTEM**
Inhibits the target enzyme in the central nervous system

**PLASMA**
Blood plasma half-life is hours

**KIDNEYS**
Metabolite is excreted

**METABOLISM**
Metabolism is via simple enzyme hydrolysis

CSF = cerebrospinal fluid.
Most frequent adverse events in a 1-year, multinational, placebo-controlled clinical trial*

- Asthenia (8% versus 4% placebo)
- Syncope (6% versus 3% placebo)
- Vertigo (8% versus 2% placebo)

*Occurring in ≥5% and at least twice the rate of placebo-treated patients.

Data on file, Eisai Inc., Teaneck, NJ.
ADVERSE EVENTS REPORTED IN CONTROLLED CLINICAL TRIALS RECEIVING RIVASTIGMINE (6-12 MG/DAY)

<table>
<thead>
<tr>
<th>Body System / Adverse Event</th>
<th>Titration</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Exelon®</td>
</tr>
<tr>
<td></td>
<td>(n = 868)</td>
<td>(6-12 mg/day)</td>
</tr>
<tr>
<td>Percent of Patients with any Adverse Event</td>
<td>66</td>
<td>86</td>
</tr>
<tr>
<td>Nausea</td>
<td>9</td>
<td>43</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>24</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9</td>
<td>17</td>
</tr>
<tr>
<td>Headache</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Confusion</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>
## Visit and Dosing Schedule

<table>
<thead>
<tr>
<th>Visit</th>
<th>Donepezil</th>
<th>Rivastigmine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Start 5 mg/day qd</td>
<td>Start 1.5 mg/day bid</td>
</tr>
<tr>
<td>Week 2</td>
<td>–</td>
<td>↑ to 3 mg/day bid</td>
</tr>
<tr>
<td>Week 4</td>
<td>↑ to 10 mg/day qd</td>
<td>↑ to 4.5 mg/day bid</td>
</tr>
<tr>
<td>Week 6</td>
<td>Telephone interview</td>
<td>↑ to 6 mg/day bid</td>
</tr>
<tr>
<td>Week 8</td>
<td>–</td>
<td>Telephone interview</td>
</tr>
<tr>
<td>Week 12</td>
<td>Study completion</td>
<td>Study completion</td>
</tr>
</tbody>
</table>

- Study medication was dosed in accordance with approved product labeling
- Dose reductions were permitted if current dose was not tolerated

Data on file. Pfizer Inc and Eisai Inc.
Memantine

• Combination treatment
  – Additional treatment with 10 mg twice daily of memantine
  – Dual-treated patients showed significantly greater improvement, and less decline
  – Less nausea and diarrhea
Treatment of Depression, Agitation, Insomnia and Hallucinations

- Avoid Tricyclic Antidepressants and Benadryl
- Insomnia: Trazadone
- Depression: SSRI’s
- Behavior problems: Aricept, Exelon, Reminyl
- Hallucinations: Resperidal, Zyprexa or Geodon
Thank You!