CURRENT AND FUTURE DIAGNOSTICS AND TREATMENTS FOR ALZHEIMER’S DISEASE 2008

Marwan Sabbagh, MD, FAAN
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Objectives:

• Define parameters and criteria for the current definition of Mild Cognitive Impairment
• Distinguish normal related memory change from mild cognitive impairment
• Discuss an algorithm for evaluation of memory loss in the non-demented elderly

DISCLOSURE
Marwan Sabbagh, MD, FAAN does have a significant financial interest or other relationship with manufacturer(s) of commercial product(s) and or provider(s) of commercial services discussed in the presentation.

Abbott, Eisai, Elan, Eli Lilly, Forest, GSK, Novartis, Pfizer, Wyeth
Current and Future Diagnostics and Treatments for Alzheimer’s Disease 2008

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Slide 2

INCIDENCE OF COMMON NEUROLOGICAL DISEASES

<table>
<thead>
<tr>
<th>Disease</th>
<th>(per 100,000)</th>
<th>(per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia</td>
<td>268</td>
<td>670,000</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>188</td>
<td>470,000</td>
</tr>
<tr>
<td>Stroke</td>
<td>200</td>
<td>500,000</td>
</tr>
<tr>
<td>Seizures</td>
<td>55</td>
<td>124,000</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>16</td>
<td>40,000</td>
</tr>
<tr>
<td>Primary neoplasm</td>
<td>15</td>
<td>37,500</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td>6</td>
<td>15,000</td>
</tr>
<tr>
<td>Primary brain tumor</td>
<td>6</td>
<td>15,000</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>2</td>
<td>5,000</td>
</tr>
<tr>
<td>Gullain Barre’s</td>
<td>1</td>
<td>2,500</td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>0.3</td>
<td>750</td>
</tr>
</tbody>
</table>
Summary of Prevalence and Impact of AD on Societal Costs

• Approximately 5.1 million Americans currently have AD
• > 100,000 people die from AD per year
• It is estimated that 14 million Americans will have AD by the year 2050
• Some studies report that Alzheimer’s disease costs $100 billion in the United States annually
• A cost of $40,000 per patient per year
• Alzheimer’s patients/families spend > $200,000 over the remainder of the patient’s life
• 10% to 30% of nursing home residents have Alzheimer’s disease

New Concept: Mild Cognitive Impairment (ICD-9: 331.83)

- **Cognitive**
  - Mild Cognitive Impairment MCI (memory)
    - 10% - 15% conversion to AD per year
    - 50% Conversion after 5 yrs (Petersen 98 Neurology; Fisk 03 Neurology)
    - >90% conversion by 10 years  (Morris 01, Neurology)
  - ApoE 4 presence biggest predictor of conversion to AD

- **Criteria**
  - Memory difficulties corroborated by informant that interfere with adaptive functioning
  - Selective deficit as measured by neuropsychological tests; other functions normal or near normal
  - Intact IADLs
  - Not demented

Table 2. Levels of Cognitive Decline From “Normal” Aging Through Alzheimer’s Disease

<table>
<thead>
<tr>
<th>Decline in cognitive function</th>
<th>“Normal” Aging</th>
<th>MCI</th>
<th>Dementia</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>previous test</td>
<td>not present</td>
<td>not present</td>
<td>not present</td>
<td>present</td>
</tr>
<tr>
<td>2 or more areas of cognitive impairment</td>
<td>not present</td>
<td>not present</td>
<td>present</td>
<td>present</td>
</tr>
<tr>
<td>Patient awareness of impairment</td>
<td>not present</td>
<td>not present</td>
<td>present</td>
<td>present</td>
</tr>
<tr>
<td>Complain of decline in cognitive function</td>
<td>not necessary</td>
<td>not necessary</td>
<td>not necessary</td>
<td>to be present</td>
</tr>
</tbody>
</table>

MCI = mild cognitive impairment; AD = Alzheimer’s disease.
Slide 9

Characterization of Alzheimer's Disease ([ICD-9: 331.0 [294.10(1)])

- Memory impairment
- More of a problem learning, rather than recall
- Once or more of:
  - Language difficulty (aphasia)
  - Visual or spatial weakness (agnosia)
  - Loss of planning or organization ability (executive dysfunction)
- Cubic error and progressive cause
- Negative laboratory evaluation

Slide 10

New Concept

- Alzheimer's disease is diagnosable in life without an autopsy
- Alzheimer's disease no longer is a diagnosis of exclusion

Slide 11

Graph showing progression of Alzheimer's disease with MMSE scores and activities of daily living (ADLs) over time.
Differential Diagnosis of Dementia

- Alzheimer's Disease (AD)
- Dementia with Lewy Bodies (DLB)
- AD & Vascular Dementia (mixed)
- Vascular Dementia
- Frontotemporal Dementia (FTD)
- Parkinson's Disease
- Huntington's Disease
- Other Degenerative Diseases (PSP, OPCA, ALS with dementia)
- Dementias Secondary to Alcohol
- Normal Pressure Hydrocephalus (NPH)
- Structural Lesions
- Metabolic Disorders (Hyperthyroidism)
- Others (e.g., neoplastic, AIDS, CJD)
- Drug/Alcohol

Dementia With Lewy Bodies (ICD-9: 331.82)

- Parkinsonism coexisting with cognitive decline
- Visual hallucinations
- Clinical fluctuations
- Neuroleptic sensitivity
- Newest criteria: REM behavioral disturbance
- Cognitive pattern may be subcortical or mixed cortical/subcortical
- More in neuropsychiatric features
- May possibly progress faster
- Pathologically characterized by worse cholinergic loss, fewer plaques and tangles, neocortical Lewy bodies, lower Braak stages.
- Treatment could include cholinesterase inhibitors and L-dopa

Vascular Dementia (ICD-9 290.40)

- May start abruptly immediately after a cerebrovascular accident
- Multi-local distribution of cognitive decline
- Focal neurologic exam
- Gait disturbances, incontinence, and fluctuating changes are common (aka Binswanger's [290.12])
- Vascular changes on imaging obligatory
- MMSE-ADREN criteria applicable
- Most vascular dementia mixed with AD
- Hachinski Score ≥ 7
- Treatment involves management of stroke risk factors and ChEIs
Slide 15

Frontotemporal Dementias (ICD-9: 331.11)

- Also known as Pick’s disease
- Now many linked to Chromosome 17 (“the tau-opathies”)
- Usually earlier age of onset compared to AD (average 40-65 years old)
- Early prominent language changes including anomia, aphasia, echolalia, and perseverative speech
- Social skills lost early
- Inappropriate behavior and judgement, disinhibition, and lack of insight
- Personality changes and withdrawal prominent
- Three subtypes now recognized (orbito-frontal variant, semantic aphasia variant, primary progressive aphasia)

Slide 16

Alcohol Related Dementias

- Three types: Korsakoff Syndrome, Marchiafava-Bignami Disease, Alcohol Dementia of Victor
- Korsakoff syndrome: Antergrade amnesia with confabulation
- Follows Wernicke’s encephalopathy
- Associated with thiamine deficiency
- Affects the mamillary bodies
- Marchiafava-Bignami disease described in Italian men
- Affects the corpus callosum
- Alcohol dementia of Victor looks like HIV dementia
- Treatment is abstinence, vitamin repletion. Usually not progressive

Slide 17

Degenerative Dementias

- AD
- DLB
- FTD
- Mixed Dementias
- Prion Diseases
- Parkinson’s Disease
- Huntington’s Disease
- Progressive Supranuclear Palsy
- Guamanian ALS-PD-AD
Slide 18

Dementias Possibly Amenable to Treatment

- Hypothyroidism
- Neurosyphilis / Infectious Etiologies
- Normal Pressure Hydrocephalus
- Vascular Dementia
- Vitamin B12 Deficiency
- Structural Lesions
- Metabolic Disorders
- Drug Intoxication
- Depression / Pseudodementia
- Wilson's Disease
- Alcohol Related Dementias

Slide 19

Dementias Associated with Other Neurological Signs and Symptoms

- AIDS (neuropathy, myopathy)
- Normal Pressure Hydrocephalus (gait disturbance, incontinence)
- Tumors / Mass Lesions (stroke-like symptoms that are subacute and evolving)
- Subdural Hematoma (stroke-like symptoms that are acute or subacute and evolving)

Slide 20

Dementias Associated with Other Neurological Signs and Symptoms

- Huntington's Disease (chorea, depression, psychosis, parkinsonism)
- Creutzfeldt Jakob Disease (myoclonus, rapid dementia, EEG changes)
- Parkinson's Disease (rigidity, bradykinesia, gait disturbance, tremor)
- B12 Deficiency (Often associated with subacute combined degeneration: proprioceptive loss, paraesthesias, hyper-reflexia)
Slide 21

Ten Warning Signs of AD

• Memory loss that affects job skills
• Difficulty performing familiar tasks
• Problems with language
• Disorientation to time and place
• Poor or decreased judgement
• Problems with abstract thinking
• Misplacing things
• Changes in mood or behavior
• Changes in personality
• Loss of initiative

Slide 22

Risk Factors for Cognitive Decline

- Age
- Genetic influences
- ApoE status
- Female gender
- Medical comorbidities

Slide 23
Slide 24

Risk Factors for Cognitive Decline:

**Medical Comorbidities**
- Hypertension
- Heart disease
- Diabetes
- Elevated low-density lipoprotein cholesterol
- High homocysteine levels
- Transitory ischemic attacks (TIAs)
- Head trauma
- Environmental exposure to toxins (particularly lead)

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Slide 25

Risk Factors for Cognitive Decline:

**Psychological/Psychosocial Factors**
- Low educational achievement
- Lack of physical activity
- Lack of social interaction/leisure activities
- Excessive response to stress (excessive cortisol levels)

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Slide 26

Risk Factors for Cognitive Decline:

**Lifestyle Choices**
- Smoking
- Substance abuse, including alcohol and illicit drugs
**Evaluation of Patients with Dementia**

**Routine**
- History
- Mental Status Exam
- Neurological Exam
- Chemistry Panel
- Complete Blood Count
- Vitamin B12 level
- Thyroid function studies
- CT/MRI

**Optional**
- Syphilis serology
- Sedimentation Rate
- Chest X-Ray
- Electrocardiogram
- Urinalysis
- Drug Levels
- HIV testing
- Lyme Serology
- EEG
- PET/SPECT
- Apo E genotyping
- CSF (Aβ42/tau or 14-3-3 for CJD)

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**Slide 28**

![Clock Drawing Test Image]

*Figure 7 Clock Drawing Test. Clock shows three examples of abstraction difficulties.*

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**Slide 29**

![Flowchart Image]

*Flowchart showing diagnosis and treatment planning for dementia.*
New Concept: Diagnosis of AD

- RPR no longer required; now considered optional; appropriate if risk factors are present
- Structural imaging is now considered a standard
- Apo E genotyping is an option
- CSF studies is an option for detection of AD and CJD
- Functional imaging now approved with restrictions

From pathology to markers

APOE Genotype Frequency and AD Risk


K-404 genotype is a risk factor for AD
Slide 33

Detection by Neuro-imaging

Slide 34

Table 1: Neurochemical genetics

<table>
<thead>
<tr>
<th>Disease</th>
<th>Chromosome</th>
<th>Gene</th>
<th>Substance</th>
<th>Commercial rating</th>
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<tr>
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<td>22</td>
<td>F27</td>
<td>insulin</td>
<td>unknown</td>
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<td>1</td>
<td>F21</td>
<td>insulin</td>
<td>unknown</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>21</td>
<td>FPP</td>
<td>insulin</td>
<td>unknown</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>11</td>
<td>APE</td>
<td>succinyl</td>
<td>unknown</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>62</td>
<td>GTPase</td>
<td>succinyl</td>
<td>unknown</td>
</tr>
<tr>
<td>PD</td>
<td>17</td>
<td>Tau</td>
<td>insulin</td>
<td>unknown</td>
</tr>
<tr>
<td>MDR1</td>
<td>20</td>
<td>Pgp</td>
<td>unknown</td>
<td>unknown</td>
</tr>
<tr>
<td>CBD</td>
<td>4</td>
<td>GLP</td>
<td>unknown</td>
<td>unknown</td>
</tr>
</tbody>
</table>
**Slide 36**

**MRI Hippocampal volume**

- Annual rate of decline in AD
  - Jack et al. 2003, Neurology
    - 4.3% decline in hippocampus vs 1.4%
  - 50% increase in temporal horn volume vs 4%
  - 59% of subjects showed decline in hippocampus volume
  - Only 60% showed decline in cognition
  - MRI is more consistent than behavioral measures.

- Power calculation
  - 1 year change: To detect a 50% effect
    - Hippocampal volume: 21 subjects per tx arm
    - Temporal horn vol: 54 subjects
    - MMSE: 241 subjects

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**Slide 37**

**Annual rate of change**

- Entorhinal cortex,
  - Du et al. 2003, Neurobiology of Aging
    - Annual rate of decline in AD of 6.5%,
    - 4.6x faster in AD

- Hippocampus
  - Cardenas et al. 2003,
    - Hippocampus: 3x faster in AD
  - Entorhinal Cortex atrophy was 3.6x faster in AD

- Global
  - Annual increase in ventricle vol. is 5.6x faster in AD.

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**Slide 38**

[Diagram of brain regions highlighted in blue]
New Concept: Use of PET in clinical practice

- FDG PET is now approved for use as a diagnostic tool for AD.
- FDG PET has a 93% positive predictive value.
- FDG PET is now covered for a ICD9 for AD.
- It is important to get prior authorization and use correct ICD 9.
- Codes that are approved include 331.11, 331.0, 290.1, 290.2, 290.3. If there is a history of cancer in the patient, use a cancer code.
- PET scans come with accompanying CT scans so other conditions can be excluded.
Slide 42

Goals for the Treatment of AD

• Improve Memory
• Improve Behavioral Symptoms
• Slow Progression
• Delay Onset

Slide 43

Slide 44

AD Therapy: Past

• Hydergine
• Cognex (Tacrine)
• Choline, Lecithin
Slide 45

AD Therapy: Present

- Aricept (Donepezil)
- Exelon (Rivastigmine)
- Razadyne (Galanthamine)
- Namenda (Memantine)
- Vitamin E
- Estrogen ?
- Anti-Inflammatories?
- Gingko Biloba?
- Folic Acid?

Slide 46

![Cholinergic Brain Systems Affected in Alzheimer’s Disease](image)

Slide 47

Use of Cholinesterase Inhibitors

- Not a panacea
- Now a standard of care
- Start early and keep using it
- Lower expectations
- May delay nursing home placement
- Consider using for neuropsychiatric features
- Modest evidence exists that switching from one to another confers any advantage
### Cholinesterase Inhibitors: Efficacy

<table>
<thead>
<tr>
<th>Cholinesterase Inhibitors</th>
<th>ACTIVITY</th>
<th>Efficacy</th>
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</thead>
<tbody>
<tr>
<td>Donepezil (Aricept)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivastigmine (Exelon)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Galanthamine (Razadyne)</td>
<td></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Cognition</th>
<th>IADLs</th>
<th>ADLs</th>
<th>Delay of functional decline</th>
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</thead>
<tbody>
<tr>
<td>Yes (ADAS and MMSE)</td>
<td>Yes (ADAS, CIBIC)</td>
<td>Yes (IDDD)</td>
<td>Yes (PDS)</td>
<td>Yes (CDR sum of boxes)</td>
</tr>
<tr>
<td>Yes (ADAS, GDS)</td>
<td>Yes (ADAS)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other Dementias</th>
<th>Yes –DLB</th>
<th>Yes – Mixed AD-VaD, VaD</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Moderate- Severe Dementia</th>
<th>Delays SNF placement, improves global function, and improves cognition (CIBIC) and behavior</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Reducing neuropsychiatric features</th>
<th>Yes (anxiety, threatening, verbal outbursts and apathy) measured by the NPI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (reduces psychosis, stabilizes aggression as measured by CIBIC, NPI). Reduces medication needs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prolonged Effect (vs projected placebo)</th>
<th>Yes (up to 5 years)</th>
<th>Yes (&gt;104 weeks)</th>
<th>Yes (48 months)</th>
</tr>
</thead>
</table>

### Slide 50

Figure 12: Demonstrates response curves for therapy with AChEIs. Please refer to the original source for detailed information on the experimental setup and results.
Slide 51

**Behavioral effects of cholinergic agents**

- Effects important in some individuals, modest at a group level
- Key effects in decreasing psychosis, apathy, agitation, and possible in anxiety
- Class specific effect
- Can treat behavior in other dementias (e.g., DLB)
- Probable synergy with psychotropics

Slide 52

**Treatment of Neuropsychiatric Features in AD**

- Delusions/Paranoia/Hallucinations (Anti-psychotics)
- Anxiety/Depression (SSRI anti-depressants, buspirone)
- Mood Stabilizers (Valproate, other anti-convulsants, cholinesterase inhibitors)
- Acute agitation (Lorazepam or other benzodiazepines, trazadone)
- Sleep disturbance (Melatonin?, trazadone). Be wary of OTC medications.
- Always consider alternatives to medication for treatment of behavioral symptoms

Slide 53

**Strategies to Facilitate Home Placement**

**Strategies for Patients**
- Specify preferences or limitations at time of diagnosis.
- Limit social activities with high risk of adverse events (e.g., hospitalizations and falls).
- Teach patient or significant other to recognize signs of agitation, such as pacing, restlessness, and agitated behavior.
- Use non-pharmacologic interventions such as music, exercise, or environmental changes.
- Encourage structured activities and routines, and maintain hygiene.
- Provide a safe and comfortable environment with adequate rest periods.
- Ensure adequate fluid intake for non-alcoholic beverages.
- Limit exposure to television and noise.

**Strategies for Caregivers**
- Participate in group care management training in caring for dementia with Alzheimer’s disease.
- Participate in caregiver support groups.
- Participate in educational seminars.

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Slide 55

**Estrogen and AD**
- Several epidemiological studies show that estrogen delays onset of AD.
- In vitro, estrogen has trophic effects on neurons and improves APP processing in a positive manner.
- Early WHI and WHIMS studies inconclusive. All adverse events occurred in the progesterone treated group.
- Follow-up WHI and WHIMS data show no protective effects of HRT against the development of AD.

Slide 56

**Anti-Inflammatories and AD**
- Inflammation found in brains of AD.
- Epidemiology suggests a decreased risk of AD in NSAID users (Zandi et al 2002 and others).
- Indomethacin first NSAID studied. Results equivocal because of high attrition rate (Rogers et al. 1993).
- Diclofenac/misoprostol showed no benefit on progression and had a high dropout rate.
- Prednisone not effective (Aisen et al. 2000).
- Four NSAIDs have gamma secretase inhibition (ibuprofen, indomethacin, diclofenac, and flurbiprofen).
- A prevention trial with NSAIDs has been completed. Results to be announced shortly (ADAPT).
Gingko Biloba and AD

- The active compounds are called flavinoids. The flavinoids are known to have free-radical scavenging properties.
- One study showed some stabilization of cognitive decline in a cohort of mixed AD and VaD patients (JAMA, October 1997).
- A prevention trial is underway (GEMS).
- A recent study of normal subjects shows no effect (JAMA, August 2002).

Folic Acid

- Framingham study confirms recently the link between elevated homocysteine levels identified as a possible risk factor for AD.
- Folic acid deficiency and homocysteine impair DNA repair in hippocampal neurons and sensitize them to amyloid toxicity in experimental models of Alzheimer’s disease.
- Protective effect of folic acid first demonstrated in the Nun Study.
- A clinical trial (VITAL) is underway to explore high dose folic acid as a treatment for AD.
Memantine

- NMDA receptor antagonist - reduces excitotoxicity
- Pivotal trials show therapeutic effect even into advanced dementia function (ADLs) and clinical impression (CIBIC)
- Clinical trials currently underway to assess synergy with ChEIs. Early results encouraging. The first trial with donepezil demonstrates superiority of the combination to donepezil alone in cognition (SIB), function (ADLs), and behavior (NPI)
- Relatively low side effects
- Long term exposure continue to show sustained effects
- Approved for treatment of moderate-severe AD

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Glutamate Hypothesis

Abnormal glutamate activity leads to sustained low-level activation of NMDA receptors

Excessive Calcium

- Neuronal death
- Cognitive decline

Slide 62
Slide 63

Slide 64

Memantine in Moderate-to-Severe AD: Cognition

SIB Score Difference

SIB Mean Change From Baseline, OC Analysis

SIB–LOCF Analysis

Farlow et al. Neurology. 2003;60(suppl 1):A412.

Slide 65

Memantine and Donepezil in Moderate-to-Severe AD: Cognitive Results

Farlow et al. Neurology. 2003;60(suppl 1):A412.
Slide 66

Table 2
Recommendations for Use of Memantine

- Initiate therapy in patients with moderate to severe Alzheimer’s disease.
- May be used in combination or coadministered with a cholinesterase inhibitor and vitamin E.
- Co-administration with a cholinesterase inhibitor is safe and well-tolerated.
- Introduce at 5 mg by mouth per day and advance at weekly intervals according to the following schedule:
  - 1 mg per day, 5 mg twice daily, 10 mg in the morning and 5 mg in the evening.
  - 10 mg twice daily.
- Monitor for side effects including headache and dizziness.
- Avoid co-administration with agents such as amantadine that have a similar mechanism of action.

Slide 67

AD Therapy: Future

- Prevention strategies (NSAIDs, estrogen, ginkgo biloba).
- Immunotherapy (active and passive).
- New cholinesterase inhibitors (Huperzine A, phenexine, Dimebon).
- Cholesterol lowering agents (atorvastatin, simvastatin).
- Anti-aggregation agents (tramiprosate, others).
- Gamma secretase modulators (Tarenflurbil, others).
- Gamma secretase inhibitors (LY-450139, MK-0249).
- Neuroprotection (Divalproex sodium).
- Chelating agents (clioquinol).
- Diabetic medications (insulin sensitizers).
- sRAGE inhibitors (TTP/Pfizer).
- Serotonin agonists (Xaliproden, others).
- GnRH agonist (Leuprolide).

Slide 68

Changes in Super Aging, Normal Aging, and Neurodegenerative Diseases

- Start AD brain changes
- MCI Clinically diagnosed AD
- Euphenic Aging
- Normal Aging
- Total loss independent function

Life Course

Birth 40 60 80 Death

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Slide 69

Prevention Trials in AD to Date

<table>
<thead>
<tr>
<th>Trial</th>
<th>(Acronym)</th>
<th>Status Intervention</th>
<th>Subject selection criteria</th>
<th>Duration (years)</th>
<th>Overall incidence rate (% per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREPARE</td>
<td>Stand-alone</td>
<td>Estrogen or Estrogen + Progestin</td>
<td>Female sex, Family history of AD, Age &gt; 65</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>ADAPT</td>
<td>Stand-alone</td>
<td>Naproxen or Celecoxib</td>
<td>Family history of dementia, Age &gt; 70</td>
<td>5 - 7</td>
<td>3 - 3.4</td>
</tr>
<tr>
<td>SYST-EUR</td>
<td>Add-on Nitrendipine and/or Enalapril and/or Hydrochlorothiazide</td>
<td>Systolic hypertension, Age &gt; 60</td>
<td>5</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>GEMS</td>
<td>Part add-on</td>
<td>Ginkgo biloba</td>
<td>Age &gt; 75</td>
<td>5</td>
<td>**</td>
</tr>
<tr>
<td>WHIMS</td>
<td>Add-on</td>
<td>Estrogen or Estrogen + Progestin</td>
<td>Female sex, Age &gt; 65</td>
<td>6</td>
<td>***</td>
</tr>
<tr>
<td>PREADVISE</td>
<td>Add-on</td>
<td>Vitamin E or Selenium or Both</td>
<td>Age &gt; 62 or &gt; 60 (if of African or Hispanic ancestry)</td>
<td>9-12</td>
<td>1</td>
</tr>
</tbody>
</table>

Slide 70

Mild Cognitive Impairment: Treatment data

- Multi-center clinical trial with conversion as primary endpoint reveals that Aricept delayed conversion by 6 months compared to placebo. Significant difference in conversion at each time point up to 20 months [Petersen et al 2005]
- Vitamin E no clinical benefit in preventing conversion to AD.
- Most robust predictor of conversion to AD is ApoE genotype
- Clinical trial with cognition as primary outcome measure demonstrated that Aricept reached statistical significant superiority to placebo on secondary endpoints [Salloway et al 2004]
- Unpublished rofecoxib study negative and may increase risk
- Unpublished galantamine and rivastigmine studies reportedly negative in primary endpoint and all interval timepoints
Slide 72

Figure 1. Etiopathogenesis of Alzheimer’s Disease

- Genetic Risk Factors
- Environmental Risk Factors
- Amyloid Precursor Protein
- Apolipoprotein E
- Amyloidogenic Protein
- Neuritic Plaques
- Cytotoxic T-Lymphocytes
- Glial Activation
- Neurofibrillary Tangles


Slide 73

Competitive Landscape for AD Treatment

- Lilly I
- Passive II
- Passive? III
- Pfizer I
- PF04360365 II
- Passive c-terminus Ab-40 III
- GSK I
- GSK933776A II
- Passive III
- Roche I
- Hucal R1450 II
- Novartis I
- Active III
- V950 II
- CAD-106 II
- Elan/Wyeth I
- Active III
- ACC-001 II
- Chelating agent III
- Alzhemed III
- Myriad: Flurizan III
- LY450139 II
- Xaliproden III
- Elan: AZD-103 II
- Wyeth
- Prana: PBT-2
- Bapineuzumab III
- TTP/PF4700

Slide 74

Future AD Treatment: Gamma secretase modulators

- R-isomer of flurbiprofen is an allosteric modulator of γ-secretase (Tarenflurbil, Flurizan)
- In vivo studies reveal reduction of insoluble Aβ in mouse brain with commensurate improvement in spatial reference learning and memory
- Reasonable safety profile with minimal gastric and renal toxicity because it does not contain anti-inflammatory effects
- Phase II trial negative but subanalysis shows sustained benefit in mild AD at the highest dose (MMSE 20-26, 800mg BID)
- Phase III trial almost completed
- Likely first disease modifying drug on the market.
Future AD Treatments: Aggregation inhibitors

- Tramiprosate (Neurochem)
- Inhibits Abeta fibrillization and reduces soluble Abeta
- Prevents Abeta formation and deposition by interfering with glycosaminoglycans. It may inhibit the inflammatory response as well.
- Phase II studies showed promising data with evidence of stabilization.
- Phase III studies just reported as negative/inconclusive in North America
- European study is ongoing

Future AD Treatments: Statins

- Based on the observation that elevated cholesterol is associated with an increased risk of AD and cholesterol is elevated in AD
- 14 epidemiological studies demonstrate a significant risk reduction of developing AD in those taking statins
- Robust scientific data demonstrating that hypercholesterolemia promotes Abeta production and deposition in a variety of animal models of AD and that cholesterol reduction strategies reduces Abeta deposition
- The first trial of its kind using HMG-CoA reductase inhibitors was concluded at Sun Health Research Institute with 98 consented, 65 enrolled and 52 completing 12 months. The treated group showed no deterioration in all scales after 12 months of treatment.
- An open label of simvastatin (Simon et al 2004) shows a similar trend but not statistically significant
- The NIA has sponsored a multi-center trial to assess simvastatin in the treatment of AD (CLASP). Results expected 2008
- Pfizer is sponsoring a second trial to assess atorvastatin in the treatment of AD (LEADe). Results expected 2008
Future AD Treatments: Immunotherapy

- AN-1792 ("the Alzheimer's vaccine") was a synthetic form of the 42 amino acid beta amyloid (Aβ) peptide
- It promotes clearance of the toxic Aβ peptide by generation of anti-Aβ antibodies
- Thirteen months subsequent to immunization, virtually all of the mice treated with AN-1792 had no detectable amyloid deposits in their brains
- In a Phase I safety study, AN-1792 was administered (multiple dosage regimens) to more than 100 patients with mild to moderate AD. It was safe and well tolerated.
- A Phase IIa clinical trial of 360 subjects stopped because of 18 cases of encephalitis, paralysis or death (US, UK, France), 5 deaths in the treatment group
- Autopsy data reveals diminution of plaques but no effects on tangles or synapse loss
- 5 year follow-up of titer positive subjects reveals a significant reduction in long-term care placement

Low plaque density: case 1+, 2+, 3+, 4+/–
Evidence that Aβ plaques had been removed temporal neocortex

unimmunized AD

immunized AD

21F12 (anti-Aβ)

Case 1

Case 2

Case 3
Slide 84

Immunotherapy (cont'd)

- Passive immunization is now being investigated (polyclonal IVIG-Baxter; monoclonal Elan/Wyeth (Bapineuzamab)
- Subjects with mild to moderate AD will undergo infusions. The schedule depends on the compound.
- Outcomes will include CBF, pharmacokinetics, and efficacy measures.
- Both approaches now in phase III.
- Other companies developing compounds include Eli Lilly, Elan and Novartis.
- Active immunization also back in development.
- These will look at smaller amyloid fragments as immunogens.
- Companies include Elan/Wyeth and Novartis/Cytos.

Slide 85

Future AD Treatments: Beta and Gamma Secretase Inhibitors

- Beta-secretase and gamma-secretase are two proteases that cleave amyloid precursor protein, producing amyloid beta-peptide.
- Early gamma secretase studies indicate predictable reduction of Aβ.

Slide 86

Cell Membrane  APP  Molcule  Cell Interior
Future AD Treatments:
Beta and Gamma Secretase Inhibitors (cont'd)

- Beta- and gamma-secretase inhibitors would block the production of beta-amyloid, which presumably would slow or halt the progression of the disease.
- Phase 1 trials have not started yet for beta secretase.
- Phase III trials slated to start Q1 2008 with Lilly (LY450139)
- Monitoring of gamma secretase inhibitors will be required for consequences of Notch inhibition (hematological)
Future AD treatments: Diabetic Medications

- Insulin resistance in AD brain
- Increased risk of AD in type II DM
- The glitazones are being investigated (Avandia (rosiglitazone) and Actos (piaglitazone))
- Mechanism of action include sensitization and potentiation of insulin activity in the brain
- They are also potent p-par gamma agonists
- In phase III studies already

Future AD Treatments: Phenserine and NS2330

- Phenserine is a reversible acetyl-selective cholinesterase inhibitor
- In vitro and in situ evidence of effect by reducing Aβ levels and secreted βAPP levels
- Animal studies demonstrate cognitive benefits without side effects
- In phase II studies
- NS2330 is a compound that enhances the function of neurotransmitters Acetylcholine, Noradrenaline, and Dopamine

New AD treatments: Dimebon

- Russian Anti-histamine. Has H1 antagonism
- Also potent AChE inhibitor and NMDA antagonist
- Phase II trials very effective symptomatically
- Entering US for phase III
**Future AD Treatments: Neurotrophic Agents**

- Intrathecal NGF infusion was a disaster!
- Cerebrolysin is believed to mimic NGF, thus generating or supporting the growth of brain cells as a neurotrophic and neuroprotective agent. It improves behavioral performance by affecting synaptic transmission in the hippocampus.
- In phase II trials, Cerebrolysin therapy led to a significant ($p < 0.001$) improvement in memory for 62% of the patients. 65% showed improvement in concentration.
- NeoTrofin (AIT-082) acts by activation of guanylyl cyclase which induces a cascade of biochemical reactions through the second messenger system leading to the production of mRNA for neurotrophins. It mimics the effects of nerve growth factor and other neurotrophins. It is in phase II trials. Phase I studies demonstrate that the drug is safe and well tolerated.
- A phase I ex vivo NGF gene therapy trial demonstrates reasonable safety. Phase II trials to start 2008.

**Future AD Treatments: Chelating Agents**

- Old anti-malarial antibiotic Clioquinol
- Clioquinol inhibits and chelates zinc and copper ions binding to Aβ
- This promotes solubilization and clearance of Aβ
- A phase II pilot study suggested that clioquinol improves cognition and lowers plasma level of Aβ42 in some patients
- One major complication is the risk of optic and peripheral neuropathy.

**Future AD Treatments: Huperzine A**

- Chinese herbal remedy for fever
- Exhibits acetylcholinesterase inhibitor properties
- Memory enhancing effects in scopolamine-impaired rats
- Clinical trials nearing completion
Slide 96

**Future AD Treatments: Valproate and Lithium**

- Both have neuroprotective properties
- They inhibit glycogen synthase kinase (GSK-3β)
- They inhibit β-Catenin (a surrogate of GSK-3β)
- They enhance bcl-2 activity (preventing apoptosis)
- Other effects on MAP kinases and CREB have been identified
- Behavioral data for AD mixed results
- Neuroprotective trial with delayed decline endpoint almost complete for divalproex sodium
- Lithium clinical trial planned

Slide 97

**Future AD treatments: Soluble RAGE inhibitors**

- RAGE (Receptor for Activated glycation endproducts)
- The receptor protein attracts Aβ
- sRAGE inhibitors reduce Aβ
- TTP488 now sold to Pfizer (aka PF4700)
- Now in phase IIb dose finding studies
- Phase Ila safety studies with good profile
- Also being investigated for Diabetes

Slide 98

**Conclusions**

- AD is evolving from a terminal disease to a chronic disease
- Future diagnosis and treatment outcomes will be driven by novel objective biomarkers
- Over 60 drugs in development for AD
Conclusion

• AD, DLB, VaD and mixed AD/VaD comprise up to 85% of dementias
• Up to 5% of dementias may have a structural etiology thus necessitating imaging on all subjects
• Clinical criteria and careful examination help discriminate dementia syndromes from one another
• Treatment may be limited but should be specifically directed toward mitigating the dementia or its untoward effects