New Research on Alzheimer’s Disease: Are We Close to Cracking the Code?

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2005 National LTCi Producers Summit
October 18, 2005
Today’s Discussion

• Current Impact of Alzheimer’s Disease
• Current Status of Research on Alzheimer’s Disease
• Potential Impact of Research Advances
• Implications for LTCI
Alzheimer's Disease: Its Impact on Individuals and the Families Who Care for Them

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MetLife Mature Market Institute
Prevalence of Alzheimer’s Disease

Source: U.S. Department of Health and Human Services, July 2002
Alzheimer’s Disease
The Personal Impact

• An estimated 4.5 million Americans have Alzheimer’s disease

• By 2050 the number of individuals with Alzheimer’s disease could range from 11.3 to 16 million

Source: Herbert, LE; Scherr, PA; Bienias, JL; Bennett, DA; Evans, DA. “Alzheimer Disease in the U.S. population; Prevalence Estimates Using the 2000 Census.” Archives of Neurology August 2003; 60 (8): 1119 – 1122.

• On average, individuals with Alzheimer’s Disease live from 8 to 10 years after diagnosis, though the disease can last for as many as 20 years

Source: Alzheimer’s Disease Education & Referral Center (ADEAR)
http://www.alzheimers.org/generalinfo.htm#howlong
Alzheimer’s Caregivers

- More likely than other caregivers to help with the most difficult ADLs such as incontinence (32% vs 13%)

- Twenty-three percent provide 40 or more hours of care per week

- Seventy-one percent have cared for the recipient for more than a year and 32% have done so for 5 or more years

Source: *Family Care: Alzheimer’s Caring in the United States, 2004*, Alzheimer’s Association and the National Alliance for Caregiving
Sacrifices of Caregiving

• Two-thirds (66%) of Alzheimer’s caregivers have sacrificed one of more of the following: time for family and friends (55%); vacations, hobbies and social activities (49%), or exercise (30%)

• Two-thirds (66%) of working caregivers have missed work because of caregiving responsibilities

• Twenty percent of caregivers are in just fair or poor health and 18% report that caregiving has made their health worse

Source: Family Care: Alzheimer’s Caring in the United States, 2004, Alzheimer’s Association and the National Alliance for Caregiving
Alzheimer’s Disease
The Financial Impact

• The national cost for caring for individuals with Alzheimer's disease is estimated at $100 billion annually

• Costs to U.S. business are more than $60 billion a year

Source: Alzheimer's Foundation of America, http://www.alzfdn.org/

• Expected that Medicare spending on people with Alzheimer’s will rise from $62 billion in 2000 to $189 billion by 2015

Source: Jon Hurdle, Alzheimer’s Spending to Triple by 2015, Health - Reuters, Yahoo News, July 19, 2004
## LTC Claims Experience

<table>
<thead>
<tr>
<th>Top Cause of Claim</th>
<th>Nursing Home</th>
<th>Home Health Care</th>
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</thead>
<tbody>
<tr>
<td><strong>By claim count</strong></td>
<td>Alzheimer’s (24.7%)</td>
<td>Cancer (17.1%)</td>
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<tr>
<td><strong>By average claim payments</strong></td>
<td>Alzheimer’s ($88K)</td>
<td>Stroke ($42K)</td>
</tr>
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<td><strong>By length of claim</strong></td>
<td>Alzheimer’s (694 days)</td>
<td>Nervous Systems (300 visits)</td>
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What Does the Future Hold?
Dementia: New and Emerging Treatments

H. Branch Coslett, MD
Professor of Neurology
University of Pennsylvania
Differential Diagnosis of Dementia

• Alzheimer’s Disease 65%

• Other Degenerative Dementias 23%
  – Lewy Body/AD 5%
  – Lewy Body Disease 7%
  – Fronto-temporal Dementia 8%
  – Cortico-basal degeneration 1%

• Vascular Dementia (Multi-infarct) 10%

• “Mild Cognitive Impairment”
Plaques and Tangles: The Hallmarks of AD

The brains of people with AD have an abundance of two abnormal structures:

- beta-amyloid plaques, which are dense deposits of protein and cellular material that accumulate outside and around nerve cells
- neurofibrillary tangles, which are twisted fibers that build up inside the nerve cell
Preclinical AD

- Signs of AD are first noticed in the entorhinal cortex, then proceed to the hippocampus.
- Affected regions begin to shrink as nerve cells die.
- Changes can begin 10-20 years before symptoms appear.
- Memory loss is the first sign of AD.
• AD spreads through the brain. The cerebral cortex begins to shrink as more and more neurons stop working and die.

• *Mild AD signs* can include memory loss, confusion, trouble handling money, poor judgment, mood changes, and increased anxiety.

• *Moderate AD signs* can include increased memory loss and confusion, problems recognizing people, difficulty with language and thoughts, restlessness, agitation, wandering, and repetitive statements.
Severe AD

- In severe AD, extreme shrinkage occurs in the brain. Patients are completely dependent on others for care.
- Symptoms can include weight loss, seizures, skin infections, groaning, moaning, or grunting, increased sleeping, loss of bladder and bowel control.
- Death usually occurs from aspiration pneumonia or other infections. Caregivers can turn to a hospice for help and palliative care.
Current Treatments: Cholinesterase Inhibitors

- Cholinergic hypothesis
- Cholinomimetics
  - lecithin, choline
  - Small effect size in meta-analyses
- Cholinesterase Inhibitors
  - tacrine (Cognex)
  - donepezil (Aricept)
  - rivastigmine (Exelon)
  - galantamine (Reminyl)
Cholinesterase Inhibitors

• First-line treatment for AD

• Approximately 1/4 show initial improvement

• Compelling evidence that slow progression
  – 6-9 months in most studies
  – May prolong time to NH placement
Current Treatments: Namenda (memantine)

- Partial NMDA receptor antagonist
- Approved for moderately severe to severe AD
- Modest but proven efficacy
  - 2-4 months
What Causes AD?

• No consensus regarding cause

• Plaques and tangles pathologic hallmark
  – Both have proponents

• Most, but not all, believe caused by accumulation of beta-amyloid
**Beta-amyloid Plaques**

1. Amyloid precursor protein (APP) is the precursor to amyloid plaque.

2. APP sticks through the neuron membrane.

3. Enzymes cut the APP into fragments of protein, including beta-amyloid.

4. Beta-amyloid fragments come together in clumps to form plaques.

In AD, many of these clumps form, disrupting the work of neurons. This affects the hippocampus and other areas of the cerebral cortex.
Beta-amyloid: Preventing senile plaques

- Inhibit production
  - Secretases
  - Statins?
  - Non-steroidal anti-inflammatory drugs?

- Block aggregation

- Enhance removal/degredation
  - Beta-amyloid transport blockers
  - Vaccines
Alzhemed

- Prevents deposition of beta amyloid
- First “disease modifying” agent
- Phase 3 trials currently
  - Slowing progression of disease
  - Appears to be well tolerated
Emerging Treatments

• Beta and Gamma Secretases
  – Secretases alter cleavage of amyloid precursor protein
  – Inhibition of secretases may decrease beta-amyloid production
  – Support from in vitro and animal models

• Generally regarded as promising approach
FIGURE 1. (A) APP; (B) Enzymatic cleavage of amyloid precursor protein (one protein fragment is Aβ); (C) Aβ accumulation in plaques.

APP=amyloid precursor protein; Aβ=amyloid.

Adapted with permission from the Alzheimer’s Disease Education and Referral Center: http://www.alzheimers.org/unraveling96.htm.
Emerging Treatments

• Vaccines against beta-amyloid
  – Passive immunization with amyloid beta 1-42 synthetic peptide in patients with mild-moderate AD
  – 6% developed meningo-encephalitis
  – Patients who developed effective titers of plaque-binding amyloid beta ABs showed slower progression
  – Autopsy of one patient revealed less plaque than expected

• Remains area of active research
Under Investigation: On the Horizon?

- Nerve growth factors
- Neuronal precursors ("stem cells")
- Statins
- Non-steroidal anti-inflammatory drugs
Early Diagnosis

• Neuropsychological investigations

• Brain Imaging
  – PET, SPECT
  – Amyloid markers
    • Univ. of Pittsburgh
    • UCLA

• Biomarkers (e.g., Abetalipoprotein E)
FIGURE 2. APP processing showing secretase products.

NH₂=amino group; KPI=Kunitz proteinase inhibitor; Aβ=β-amyloid; COOH=carboxyl group; APP=amyloid precursor protein.

Adapted and used with permission from Davis KL. Department of Psychiatry, Mount Sinai School of Medicine.
Antioxidants

- Reduce oxidative injury to brain
- Sano et al, NEJM 336: 1216-22
  - Vitamin E 1000 IU BID, selegiline, both or placebo in 341 patients with moderate AD
  - Vitamin E and selegiline delayed time to end-point of institutionalization or impaired ADLs by average of approximately 8 months
  - No effect on measures of cognition
- Vitamin E 1000 IU often recommended
Pharmacologic Interventions

• Less is more
  – Indication for medication must be compelling

• Careful history of medications
  – Anxiolytics,
  – Hypnotics
  – OTC sleep and cold preparations
Cholinesterase Inhibitors

• Generally well tolerated
• Side Effects
  – Nausea, diarrhea, weight loss
  – Can cause insomnia
• Will often tolerate if use slower dose escalation
Neurons have an internal support structure partly made up of microtubules. A protein called *tau* helps stabilize microtubules. In AD, *tau* changes, causing microtubules to collapse, and *tau* proteins clump together to form neurofibrillary tangles.
The Changing Brain in Alzheimer’s Disease

No one knows what causes AD to begin, but we do know a lot about what happens in the brain once AD takes hold.
AD Research: Finding New Answers and Asking Better Questions

• The Search for Causes (slides 24 – 28)
• Diagnosing AD (slides 29 – 30)
• Clinical Trials (slide 31)
• The Search for Treatments (slides 32-33)
• New NIA Study (slide 34)
• Managing the Symptoms of AD (slide 35)
AD Research: the Search for Causes

• AD develops when genetic, lifestyle, and environmental factors work together to cause the disease process to start.

• In recent years, scientists have discovered genetic links to AD. They are also investigating other factors that may play a role in causing AD. NIA-funded Alzheimer’s Disease Centers (ADCs) across the country are leading the research efforts looking into causes, diagnosis, and treatment of AD.
AD Research: the Search for Causes

Late-onset AD Genetics Study

- Partnership between the NIA and the Alzheimer’s Association
- Need to recruit a total of 1,000 families to find the remaining late-onset risk factor genes
- 2 or more living siblings with AD
- One other living family member with or without AD
- Contact: e-mail: alzstudy@iupui.edu or Website: www.ncrad.org
AD Research: the Search for Causes

Studies at the Cellular and Molecular Level

- Oxidative damage from free radical molecules can injure neurons.

- Homocysteine, an amino acid, is a risk factor for heart disease. A study shows that an elevated level of homocysteine is associated with increased risk of AD.

- Scientists are also looking at inflammation in certain regions of the brain and strokes as risk factors for AD.
AD Research: the Search for Causes

Genetic Studies

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.
Research in Alzheimer’s Disease

How and When Will It Impact the LTCI Market?

Bill Bigelow, FSA
Producers Summit
MetLife
2005
The Current Impact of Alzheimer’s Disease

- Alzheimer’s Disease (AD) is the most frequent cause of claim

- AD claims are the longest lasting claims

- AD claims are the most expensive claims

Source: Society of Actuaries, Long Term Care Experience Committee, Intercompany Study 1984-2001
And....

- AD claims are trending upward

- AD claims are more likely to still be open claims

- AD claims that are closed are more likely to have been closed due to death than due to recovery or expiration of benefits.

Source: Society of Actuaries, Long Term Care Experience Committee, Intercompany Study 1984-2001
ICD-9 Codes (SOA study classification)

- 290–294: Organic Psychotic Conditions
- 331: Alzheimer’s Disease and other cerebral degenerations
- 797: Senility without psychosis, senescence
Considering the Impact - Diagnosis and Treatment

◆ Claims coded with AD and other dementia (SOA)
  - at least 40% of all facility claim dollars
  - at least 20% of all home care claim dollars

◆ Of these, 60–70% may be related to AD

Based on MetLife pricing model-

◆ With a guaranteed cure in
Considering the Impact - A More Likely Scenario

- Research evolves over next 10 years
- Resulting in every AD claim being delayed by 3 years
- Premiums could be lowered by 6%

Based on MetLife pricing model.
What will we know and when?
Remember that ...

◆ Many other changes will be occurring over the same time period

◆ Medical and scientific advancement is usually incremental

◆ LTC trends will be slow to develop and to recognize
Reserves may be more important than claims

- Insurance regulators are prohibiting expectation of “morbidity improvement” in statutory reserves
  (Conservative reserves are probably a good thing.)

- Reserve assumptions are traditionally “locked”
Issues impacting pricing decisions

- New versus existing business
- Earnings trends as well as claim trends
- Capital and investment markets
Evolving the Product

- AD testing technology

- Changes in AD treatment will lead to changes in LTCI product design

- Future changes in financing medical care will be critical as well