New Drugs in Alzheimer’s Disease

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Genetic scientists reveal biggest breakthrough for 15 years

ALZHEIMER’S: A MASSIVE LEAP

Barnardo’s chief: Take babies from bad parents

The Independent, 7 September, 2009
PILL TO BEAT ALZHEIMER'S

New treatment will stop disease for three years

Kate, Wills and Harry's princely sum for charity

Daily Express, 18 July, 2012
Drug giants give up on Alzheimer’s cure

Research too difficult and costly, say pharmaceutical companies

By JEREMY LAURANCE
Health Editor

The world’s leading pharmaceutical companies are downgrading the search for new treatments for Alzheimer’s disease after the failure of a series of high-profile drugs trials. The human and financial costs of the disease are growing rapidly as the population ages, but the prospects of treatments to halt it, or slow its progress, are receding as at least five trials in the past five years have delivered disappointing results.

This year, a trial of Duzon, backed by Pfizer, the US pharmaceutical giant, and reported in January, failed to show any benefit, instead costing the company $760m in lost investment. In July, bapineuzumab, developed by Irish drug-maker Elan in association with Pfizer and the US multinational Johnson & Johnson, also failed to show an impact on symptoms.

In August, another US group, Eli Lilly, reported the failure of solanezumab, its second Alzheimer’s drug to disappoint in two years. In 2010, a trial of semagacestat not only failed to slow the disease but worsened symptoms.

The setbacks have damaged confidence among drug makers in the field of neuroscience – brain research – which was already shaky.

Pharmaceutical manufacturers worldwide are under pressure and have been cutting back in the recession, but neuroscience has been disproportionately hit with AstraZeneca, Pfizer, Merck, Sanofi, Novartis and GlaxoSmithKline all downsizing.

Capita to be paid bounty for catching illegal immigrants

By NIGEL MORRIS
Deputy Political Editor

Ministers were accused last night of placing a "bounty" on illegal immigrants’ heads after the UK Border Agency announced that a private company will be brought in to track down more than 170,000 people still in the country after their visas expired.

Capita will be paid up to £200m on a payment-by-results basis.

The Independent, 19 September, 2012
Where are we now?

- Current medications for Alzheimer’s Disease are only modestly effective
- Recent data (summer ‘12) on big clinical trials on two drugs, Bapineuzumab and Solanezumab, were disappointing
- Our understanding of Alzheimer’s disease has advanced hugely over the last 30 years
  - Translating our understanding into new drugs remains the challenge
Outline of Presentation

• Introduction to Alzheimer’s Disease
• The Drug Discovery Process
• Current Drugs for Alzheimer’s Disease
• Amyloid-related drugs for Alzheimer’s Disease
  ➢ Segamacestat
  ➢ Bapineuzumab, Solanezumab
• What happens next?
Alzheimer’s is the Most Common Form of Dementia

<table>
<thead>
<tr>
<th>Cause</th>
<th>Occurrence %</th>
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<tbody>
<tr>
<td>Alzheimer’s disease (AD)</td>
<td>57</td>
</tr>
<tr>
<td>Vascular dementia (VD)</td>
<td>13</td>
</tr>
<tr>
<td>Depression</td>
<td>4.5</td>
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<tr>
<td>Alcohol</td>
<td>4.2</td>
</tr>
<tr>
<td>Normal pressure hydrocephalus</td>
<td>1.6</td>
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<tr>
<td>Metabolic and medications</td>
<td>3.0</td>
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<tr>
<td>Neoplasm</td>
<td>1.5</td>
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<tr>
<td>Parkinson’s disease</td>
<td>1.2</td>
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<tr>
<td>Huntington’s disease</td>
<td>0.9</td>
</tr>
<tr>
<td>Mixed AD and VD</td>
<td>0.8</td>
</tr>
<tr>
<td>Infection</td>
<td>0.6</td>
</tr>
<tr>
<td>Subdural hematoma</td>
<td>0.4</td>
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<tr>
<td>Post-trauma</td>
<td>0.4</td>
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<tr>
<td>Other</td>
<td>7.1</td>
</tr>
<tr>
<td>Not demented</td>
<td>3.7</td>
</tr>
</tbody>
</table>
Alzheimer’s Disease – A Growing Problem

Slide courtesy of Eric Karran, Scientific Director, Alzheimer’s Research UK

WHO/Alzheimer’s Disease International 2012
Alzheimer’s Disease Costs – 2007-8 Figures

“At least 12 times as much was spent on cancer research as dementia research, yet dementia cost the country twice as much as cancer”

E. Karran, The Independent, 19th September, 2012

Slide courtesy of Eric Karran, Scientific Director, Alzheimer’s Research, UK
Amyloid and Alzheimer’s Disease

Auguste D. (age 51) admitted in to an asylum in 1901 due to “delerium and frenzied jealousy of her husband”

Alzheimer attempted to relate clinical symptoms to pathological changes (1906)
Alzheimer’s Disease – A Brief History

1906  Alzheimer’s first description of Alzheimer’s Disease
1968-1970  dementia not merely due to hardening of the arteries
1976  reduced levels of acetylcholine neurotransmission demonstrated
1984  composition of amyloid protein identified
1991  a gene associated with Alzheimer’s Disease identified
   ➢  This and other genes are involved with the production of amyloid
   ➢  The “amyloid hypothesis” has dominated recent therapeutic strategies
1993  ApoE identified as a risk factor
2009  Additional (small) AD risk factors identified
2012  APP mutation reported to be afford protection against AD
Diagnosis of Alzheimer’s Disease

1. Diagnose dementia

2. Rule out others possible causes of dementia
   - Possible AD (atypical clinical features, no other cause, no histology)
   - Probable AD (typical clinical features without histology)
   - Definite AD (clinical diagnosis with histological confirmation)

Typical clinical features
   - Memory impairment
   - Loss of language
   - Visuospatial deficits (e.g. drawing)
   - Motor and sensory abnormalities, gait disturbances only in latter stages
   - Duration can vary from 2-3 years to 15-20 years
Measuring Disease Severity

- There are a variety of tests of cognitive function
  - Alzheimer’s Disease Assessment Scale – Cognition subscale (ADAS-Cog)
  - Blessed dementia rating scale
  - Cambridge Neuropsychological Test Automated Battery (CANTAB)
  - Mini-mental state exam (MMSE)
  - Neuropsychiatric Inventory (NPI)

- Activities of daily living ratings scales
  - Disability Assessment for Dementia (DAD)
  - Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL)
  - ADCS-Clinical Global Impression of Change (ADCS-CGIS)
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The Drug Discovery Process

35 New Drug Approvals in 2011
$50 billion 2011 R&D expenditure
• 50/35 = $1.4 billion/drug approval
Clinical Trials for New Drugs

**WATCHING YOUR STEP – THE DIFFERENT STAGES OF CLINICAL DEVELOPMENT AND WHAT THEY EXAMINE**

**PHASE I**
- Checking for safety
- Sample: 10-20 healthy volunteers
- Unexpected side effects may occur
- £10 m
- 50:50 chance

**PHASE II**
- Checking for efficacy
- Sample: about 200 patients
- Most research projects fail in Phase II due to product not being as effective as anticipated
- £25 m
- 1:3 chance

**PHASE III**
- Confirm findings in large patient population
- Sample: more than 1,000 people
- Likelihood to detect rare side effects increases with number of people involved
- £100 m
- 2:3 chance

**PHASE IV**
- Testing long-term safety in diverse patient population
- Sample: "real life patients" – testing being carried out outside of clinical environment (post-marketing studies)
- Previously untested groups may show adverse reactions

Source: AGCS

http://www.agcs.allianz.com/assets/PDFs/GRD/GRD%20individual%20articles/GRD_02_09_en%20Clinical%20Trials.pdf
The Drug Discovery Process in Pictures
Disease Modification vs Symptomatic Relief

- Disease modification needs understanding of pathology
  - Possible for neurodegenerative but not psychiatric disorders

Pengalos et al., 2007, Nat. Rev. Drug Discov., 6:521-532
General Strategies for Drug Discovery

- Serendipity
- Drug repositioning
- Take an existing drug and make it better
- Hypothesis-driven drug discovery based on an understanding of the disease process
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Overview of Alzheimer’s Disease Drugs

- ↓ Aβ production
- ↓ Aβ aggregation
- ↑ Aβ clearance (immunotherapy)
- ↓ tau aggregation or phosphorylation
- Cholinergic drugs
- Others

Mangialasche et al., 2010 Lancet Neurol., 9:702-716
Alzheimer’s Disease Drugs - Where Are We Now?

- IVIg = intravenous immunoglobulins
- EGCg = epigallocatechin-3-gallate (polyphenol from green tea)

Mangialasche et al., 2010
Lancet Neurol., 9:702-716
Treating the Symptoms – Understanding the Chemistry of the Brain

Many (>50) different chemicals involved

- **Acetylcholine**
- Dopamine
- Serotonin
- Noradrenaline
- Glutamate
- GABA
- Etc. etc
4 FDA-approved drugs for Alzheimer’s Disease

Acetylcholinesterase (AChE) inhibitors
- Prevent the breakdown of acetylcholine
- 3 approved AChE inhibitors
  - Donepezil (Aricept) (Eisai/Pfizer) – FDA approval Dec 1996
  - Galantamine (Razadyne or Reminyl) (Forest/Janssen) – FDA approval Feb 2001
    - Originally isolated in the 1950s from snowdrops (Galanthus species)
  - Rivastigmine (Exelon) (Novartis) – FDA approval Apr 2000

N-Methyl-D-aspartate (NMDA) receptor antagonist
- Supposedly prevents glutamate-related neurotoxicity
  - Memantine (Namenda) (Merz/Forest & Lundbeck) – FDA approval Oct 2003
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Disease Modification – Understanding How and Why Nerve Cells Dies

Potential clues to the disease process come from:

- Are there pathological changes in the brain and if so, what are they?
  - Plaques and tangles
  - Geography (environment), families (genetic)
  - If yes, do we understand these clusters?

- Are there “risk factors” associated with aging?
  - Aging, ApoE
  - If yes, do we understand these clusters?
Senile plaques contain a 40-42 amino acid protein called amyloid
Modifying the Disease – Understanding What Goes Wrong in Alzheimer’s Disease - 2

Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer’s disease

Alison Gaote*, Marie-Christine Chartier-Harlin†, Mike Mullan*, Jeremy Brown*, Fiona Crawford*, Liana Fidani*, Luis Glufla†, Andrew Haynes‡, Nick Irving*, Louise James*, Rebecca Manti†, Philippa Newton*, Karen Rook‡, Penelope Roques*.

Early-onset Alzheimer's disease caused by mutations at codon 717 of the β-amylloid precursor protein gene

Marie-Christine Chartier-Harlin, Fiona Crawford, Henry Houlden, Andrew Warren*, David Hughes, Liana Fidani, Alison Gaote, Martin Ressor, Penelope Roques, John Hardy & Mike Mullan

Familial AD is associated with mutations in amyloid
Placing Your Bets – Amyloid in AD

Reduce Aβ formation
a  GPCR modulation of APP processing
b  BACE1 inhibition
c  γ-secretase
   GS inhibitor, GS modulator

Increase Aβ clearance
d  Activate Aβ degrading enzymes
   Neprilysin, insulin-degrading enzyme
e  Modulation of gene transcription
f  Antibodies
   Bapineuzumab, Solanezumab

Other approaches
g  Aggregation inhibitors

Pangalos et al (2007)
Nat. Rev. Drug Discov., 6:521-532
Alzheimer’s Disease Drugs - Where Are We Now?

Mangialasche et al., 2010 Lancet Neurol., 9:702-716
Semagacestat – γ-Secretase Inhibitor

- γ-secretase inhibition should reduce amyloid
  - deterioration in cognition should slow down

Lilly Halts Development of Semagacestat for Alzheimer's Disease Based on Preliminary Results of Phase III Clinical Trials

Posted August 17, 2010

Decision does not affect other Lilly Alzheimer's compounds in development

INDIANAPOLIS, Aug. 17 /PRNewswire-FirstCall/ -- Eli Lilly and Company (NYSE: LLY) will halt development of semagacestat, a gamma secretase inhibitor being studied as a potential treatment for Alzheimer's disease, because preliminary results from two ongoing long-term Phase III studies showed it did not slow disease progression and was associated with worsening of clinical measures of cognition and the ability to perform activities of daily living.

- Semagacestat (LY450139) studies stopped following interim analysis
  - Cognition became worse and skin cancer incidence increased
  - Not clear why Semagacestat had these effects
Alzheimer’s Disease Drugs - Where Are We Now?

Mangialasche et al., 2010 Lancet Neurol., 9:702-716
Alzheimer’s Disease Drugs - Where Are We Now?

Mangialasche et al., 2010 Lancet Neurol., 9:702-716
Bapineuzumab – Phase 3 Failure

UPDATED: Pfizer, J&J kill PhIII program for key Alzheimer's drug
August 6, 2012 | By Ryan McBride

Pfizer ($PFE) and Johnson & Johnson ($JNJ) have nixed development of one of the most closely watched drugs in their pipelines, bapineuzumab, after two Phase III clinical trials for the experimental Alzheimer’s therapy ended in failure. The decision comes as no surprise as the program was given slim odds of success. But many are following bapi, one of the most advanced drugs for combating beta amyloid that builds up in the brain and is a suspected cause of the common memory-stealing disease.

Trouble for the program surfaced last month after bapi fell short in improving a key measure of cognition compared with placebo in a Phase III trial involving Alzheimer’s patients who are ApoE4 gene carriers. On Monday, the companies reported that the second of four late-stage studies of the drug--this one involving patients with ApoE4 non-carriers--failed as well. And they have decided to end all trials for the drug from Irish drugmaking partner Elan ($ELN), ceasing development of their blockbuster hopeful.
Disease Modification vs Symptomatic Relief

Pengalos et al., 2007, Nat. Rev. Drug Discov., 6:521-532
Bapineuzumab – Phase 3 ADAS-Cog

Improvement

Mean (+/-SE) Change From Baseline

Weeks

MMRM (mixed model for repeated measures) analysis. Error bars represent 1 SE.
Solanezumab - Phase 3 Failure

Topics: Clinical Trials

Lilly's Alzheimer's drug solanezumab flunks out, but CEO sees promise

August 24, 2012 | By John Carroll

After enduring months of criticism about its late-stage effort to determine the efficacy of the last big Phase III hope for Alzheimer's, Eli Lilly ($LLY) this morning announced that solanezumab flunked both primary endpoints. The failure, widely forecast by a long lineup of analysts, will raise more doubts about the theory that cutting levels of toxic amyloid beta in patients with mild to moderate Alzheimer's can help patients with the disease.

Lilly, though, isn't giving up on the drug, its second major try at treating Alzheimer's. CEO John Lechleiter, who has bet his job that the company's R&D division can develop a new generation of therapies, noted that a secondary analysis of pooled data "showed statistically significant slowing of cognitive decline in the overall study population of patients with mild-to-moderate Alzheimer's disease. In addition, pre-specified secondary subgroup analyses of pooled data across both studies showed a statistically significant slowing of cognitive decline in patients with mild Alzheimer's disease, but not in patients with moderate Alzheimer's disease."
Alzheimer’s Disease Drugs - Where Are We Now?

Mangialasche et al., 2010 Lancet Neurol., 9:702-716
Pictorial Summary of Recent Clinical Data
Drug giants give up on Alzheimer’s cure

Research too difficult and costly, say pharmaceutical companies

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Full report, PAGE 18

Continued on PAGE 6

The Independent, 19 September, 2012
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Drugs for Testing Amyloid Hypothesis

2 interpretations of the data

• Drugs not good enough
  ➢ Use drugs that are better than bapineuzumab, solanezumab and segamacetat

• Drugs are good enough but we need to use them much earlier
  ➢ Evaluate drug in prevention trials
Drug Treatment – Timing is Everything

Hypothetical model of dynamic biomarkers of the Alzheimer’s pathological cascade


• ADNI provides an in vivo view on disease progression
  ➢ Amyloid pathology might be complete by the time symptoms occur
Alzheimer’s Disease Prevention Trial

- Can drug treatment prevent AD occurring in a family with APP mutation?
  - Columbian family with γ-secretase presenilin-1 E280A mutation
  - 3-arm, 5-year study
    - 100 E280A family members receive placebo
    - 100 E280A family members receive Genentech Crenezumab antibody
    - 100 non-E280A family members receive placebo
  - Philanthropic (Banner Institute), public (NIH) and private (Genentech) funding of roughly $15:$16:$65 million
Alzheimer’s Disease Neurofibrillary Tangles

- Neurofibrillary tangles (NFTs) contain paired helical filaments
  - hyperphosphorylated tau (2-3 phosphates → 8-9 phosphates)

Summary

- The last 30 years have seen huge advances in our understanding of Alzheimer’s Disease
- The amyloid hypothesis has dominated recent drug discovery efforts
  - Several high-profile failures
  - Each failure is a lesson learned
- Our understanding of Alzheimer’s disease has advanced despite rather than because of research funding
Alzheimer’s Disease Costs – 2007-8 Figures

Slide courtesy of Eric Karran, Scientific Director, Alzheimer’s Research, UK