Perspectives from the Alzheimer’s Association

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Alzheimer’s & Related Dementias

DEMENTIA
An “umbrella” term used to describe a range of symptoms associated with cognitive impairment.

ALZHEIMER’S 50%-75%
VASCULAR 20%-30%
LEWY BODIES 10%-25%
FRONTOTEMPORAL 10%-15%

MIXED DEMENTIA = >1 NEUROPATHOLOGY - PREVALENCE UNKNOWN
Alzheimer’s – Plaques & Tangles

[Image of photographs and a microscopic view highlighting plaques and tangles]
Risk Related to Cognitive Decline & Alzheimer’s

- **Age:** The greatest known risk factor
- **Heart-head connection**
  - Increased risk suspected if high blood pressure, heart disease, stroke, diabetes and high cholesterol
- **Head injury**
- **Genetic risk (APOE4)**
Statement of Evidence: Modifiable Risk Factors for Cognitive Decline & Dementia

(1) Regular physical activity and management of cardiovascular risk factors (diabetes, obesity, smoking, and hypertension) have been shown to reduce the risk of cognitive decline and may reduce the risk of dementia;

(2) Healthy diet and lifelong learning/cognitive training may also reduce the risk of cognitive decline;

(3) There are still many unanswered questions and significant uncertainty with respect to the relationship between individual risk factors and dementia.
10 Ways to LOVE Your Brain
Continuum of Alzheimer’s Disease

Normal Alzheimer’s disease

Adapted from Sperling et al. 2011
PET Amyloid Imaging

Alzheimer's Disease

Normal Aging

Figures courtesy of Drs Keith Johnson/ Reisa Sperling
Possible Prevention of Alzheimer’s?

**Primary Prevention**
- Delay onset of AD pathology
- Decrease Aβ₄₂ production
- Prevent tangle formation

**Secondary prevention**
- Delay onset of cognitive impairment in individuals with evidence of pathology
  - Decrease accumulated Aβ burden
  - Decrease neurodegeneration with anti-tau or neuroprotective agents

**Tertiary prevention and treatment**
- Delay onset or progression of dementia
  - Neuroprotection-prevent neuronal loss
  - Enhance function of remaining neurons
  - Neurotransmitter repletion

Clinical disease stage:
- Normal
- No pathology
- Preclinical
- MCI
- Dementia
Current Alzheimer’s Therapies: Symptomatic

**Cholinesterase Inhibitors**
- Tacrine (Cognex)
- Donepezil (Aricept)
- Rivastigmine (Exelon)
- Galantamine (Razadyne)

**Glutamate Moderators**
- Memantine (Namenda)

**Combination Therapies**
- Donepezil & memantine (Namzaric)
Clinical Drug Development Pipeline for Alzheimer’s Disease

### Pipeline Comparison

- **HCV**
  - Preclinical: 30.2
  - Phase I: 10.5
  - Phase II: 6.6
  - Phase III: 1.7
  - Registration: 1.1
  - Launch: 1.0
  - Overall success rate: 2.0%

- **Alzheimer’s Disease**
  - Preclinical: 119.3
  - Phase I: 33.6
  - Phase II: 23.0
  - Phase III: 5.8
  - Registration: 1.0
  - Launch: 1.0
  - Overall success rate: 0.5%

- **MRSA**
  - Preclinical: 13.0
  - Phase I: 4.7
  - Phase II: 2.9
  - Phase III: 1.8
  - Registration: 1.1
  - Launch: 1.0
  - Overall success rate: 4.6%

- **Industry average**
  - Preclinical: 14.6
  - Phase I: 8.6
  - Phase II: 4.6
  - Phase III: 4.6
  - Registration: 1.1
  - Launch: 1.0
  - Overall success rate: 4.1%
Therapeutic Agents in Phase I and II Clinical Trials for Alzheimer’s Disease

- AADvac1
- ABT-957
- Aducanumab (BIIB 037)
- Allopregnenalone
- BI 409306
- Crenezumab (MABT5102A)
- CT1812
- Curcumin
- DBS-f (Deep brain stimulation - fornix)
- GC021109
- Insulin
- JNJ-54861911
- KHK6640
- Lu AF20513
- LY3002813
- LY3202626
- MEDI1814
- PF-06751979
- S-Equol
- TPI-287
- Transcranial direct current stimulation (tDCS)
- Transcranial magnetic stimulation (TMS)
- ANAVEX2-73
- Atomoxetine
- AZD0530
- BAN2401
- BI 409306
- Blood plasma
- CNP520
- CPC-201
- Crenezumab (MABT5102A)
- DAIO-B
- D-ribose
- E2609
- Exendin-4
- Genistein
- Insulin
- Insulin Glulisine
- IV Ig
- JNJ-54861911
- Ladostigil
- Levetiracetam
- Lipoic Acid
- Liraglutide
- Mesenchymal stem cells
- MK-7622
- Nicotinamide
- n-PUFA
- Omega-3
- PQ912
- PXT00864
- Rasagiline
- RO4602522
- RPh201
- Sargramostim
- Simvastatin
- SUVN-502
- T3D-959
- T-817MA
- Transcranial magnetic stimulation (TMS)

As of 12/2015
Therapeutic Agents in Phase III Clinical Trials for Alzheimer’s

Aducanumab
Biogen
Antibody to beta amyloid
ALZT-OP1
AZTherapeutics
Drug combination
AZD3293
Astrazeneca
BACE inhibitor
Azeliragon
TransTech Pharma
Inhibits receptor for advanced glycation end-products
Encenicline/MT-4666
Forum Pharmaceuticals
Mitsubishi/Tanabe
Pharmaceutical Corp.
Nicotinic receptor agonist
Gantenerumab
Hoffman-La Roche
Monoclonal antibody against beta-amyloid
Part of DIAN-TU
Insulin
Alzheimer’s Disease Cooperative Study
IVIg and Albumin
Grifols
Intravenous immunoglobulin
LU AE58054
H. Lundbeck
5HT6 receptor antagonist
Masitinib
AB Science
Inhibitor of c-KIT cell signaling
Nilvadipine
St. James Hospital
Calcium Channel Blocker
Pioglitazone
Takeda
PPAR-gamma activator
Sodium Oligo-mannurate (GV-971)
Shanghai Greenvalley Pharmaceuticals
Inhibits beta-amyloid aggregation
Solanezumab
Eli Lilly
Humanized Ab against amyloid
TRx0237
TauRX
Tau aggregation inhibitor
Verubecestat (MK8931)
Merck
BACE inhibitor

As of 12/2015
Experimental Drug Trial Results: Potential Disease Modifying Treatments

• **Solanezumab (Lilly)**
  – New analysis of results from two prior phase 3 studies suggests it may slow cognitive decline
  – On-going Phase 3 used Amyloid PET to enroll participants

• **Aducanumab (Biogen)**
  – Small Phase 1b suggests may slow cognitive decline in people w/ mild Alzheimer’s
  – Launched two Phase 3 clinical trials using Amyloid PET to enroll participants
Experimental Drug Trial Results: Potential Symptomatic Treatments

- **RVT-101 (Axovant)**
  - Suggests improvement in cognition when added to donepezil (Aricept)
  - Announced plans to launch Phase 3

- **AVP-923: Dextromethorphan/Quinidine (Avanir)**
  - Significant improvement in agitation
  - Determining next steps
THE END OF ALZHEIMER’S STARTS WITH YOU