Up-date on Alzheimer's Disease Medications and Research

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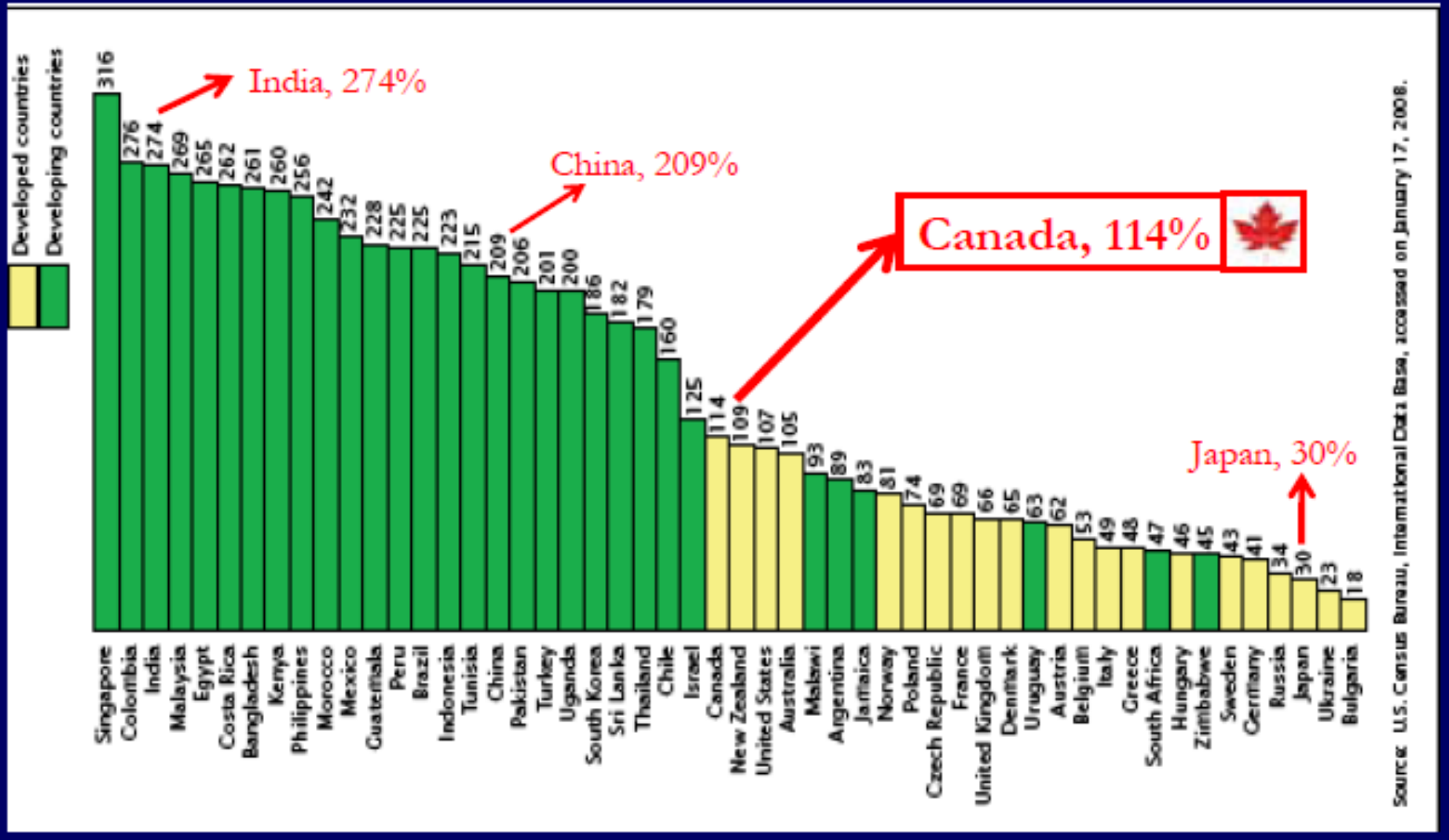
Outline

- Background on aging population
- Clinical Case
- Review/update on current meds - AcHEI's, memantine - place in therapy
- New agents in research
- Other options
- Summary

% increase in 65+ population 2008 to 2040



Source: Ganguli, M."Dementia as a global problem", 5th CCD, Toronto, 2009

The Leading Causes of Disability: Established Market Economies, 1990

	Cost (millions $)	% of Total
Major depression	6.7	14.3
Alcohol use	4.5	9.6
Osteoarthritis	2.7	5.8
Dementia /degenerative brain disease	2.4	5.1
Schizophrenia	2.2	4.7
Bipolar disorder	1.7	3.6
Cerebrovascular	1.6	3.3
Diabetes	1.5	3.2
OCD	1.5	3.1
Drug use	1.4	3.0

Murray and Lopez 1996

Source: Ganguli, M."Dementia as a global problem", 5th CCD, Toronto, 2009

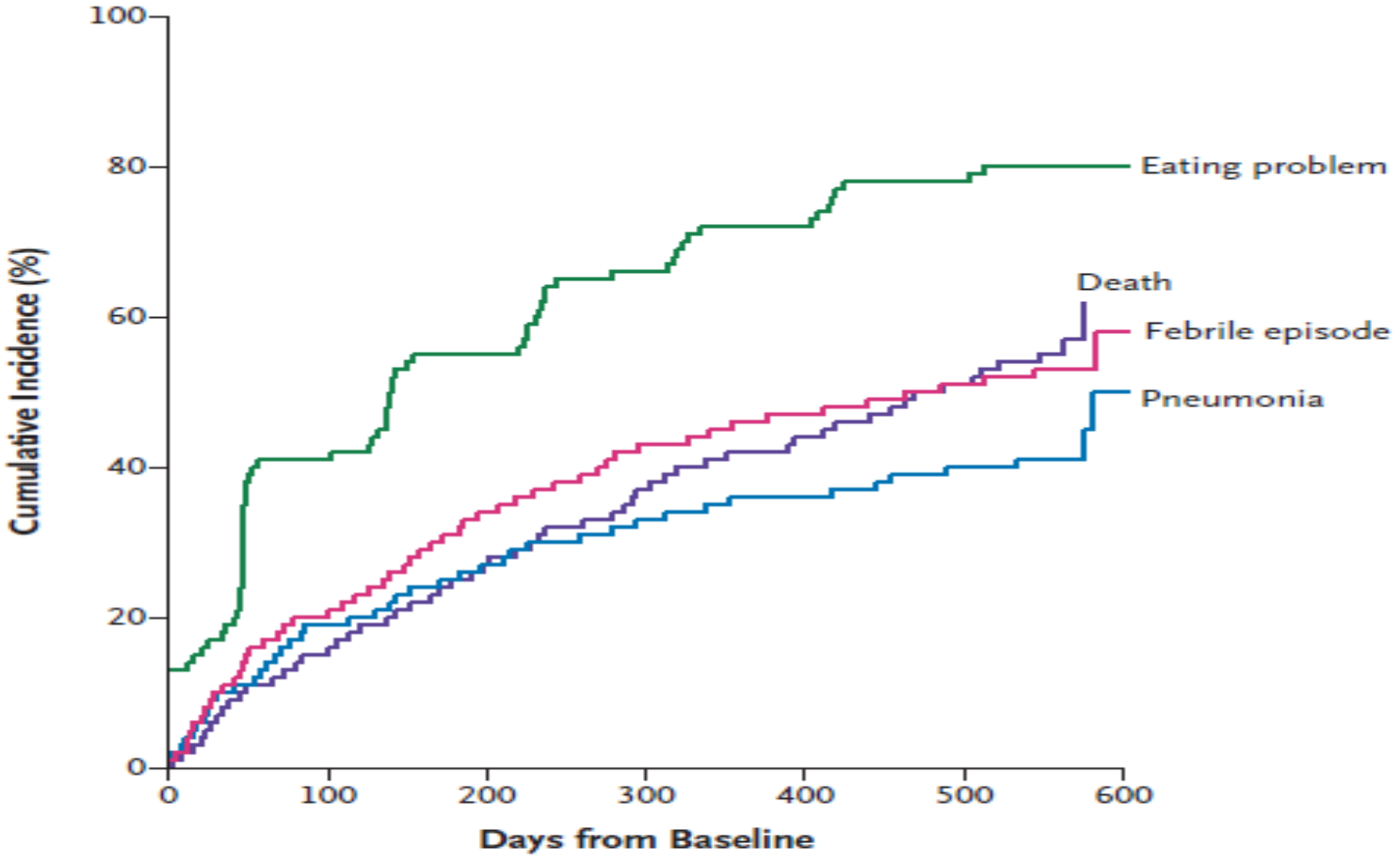


Figure 1. Overall Mortality and the Cumulative Incidences of Pneumonia, Febrile Episodes, and Eating Problems among Nursing Home Residents with Advanced Dementia.

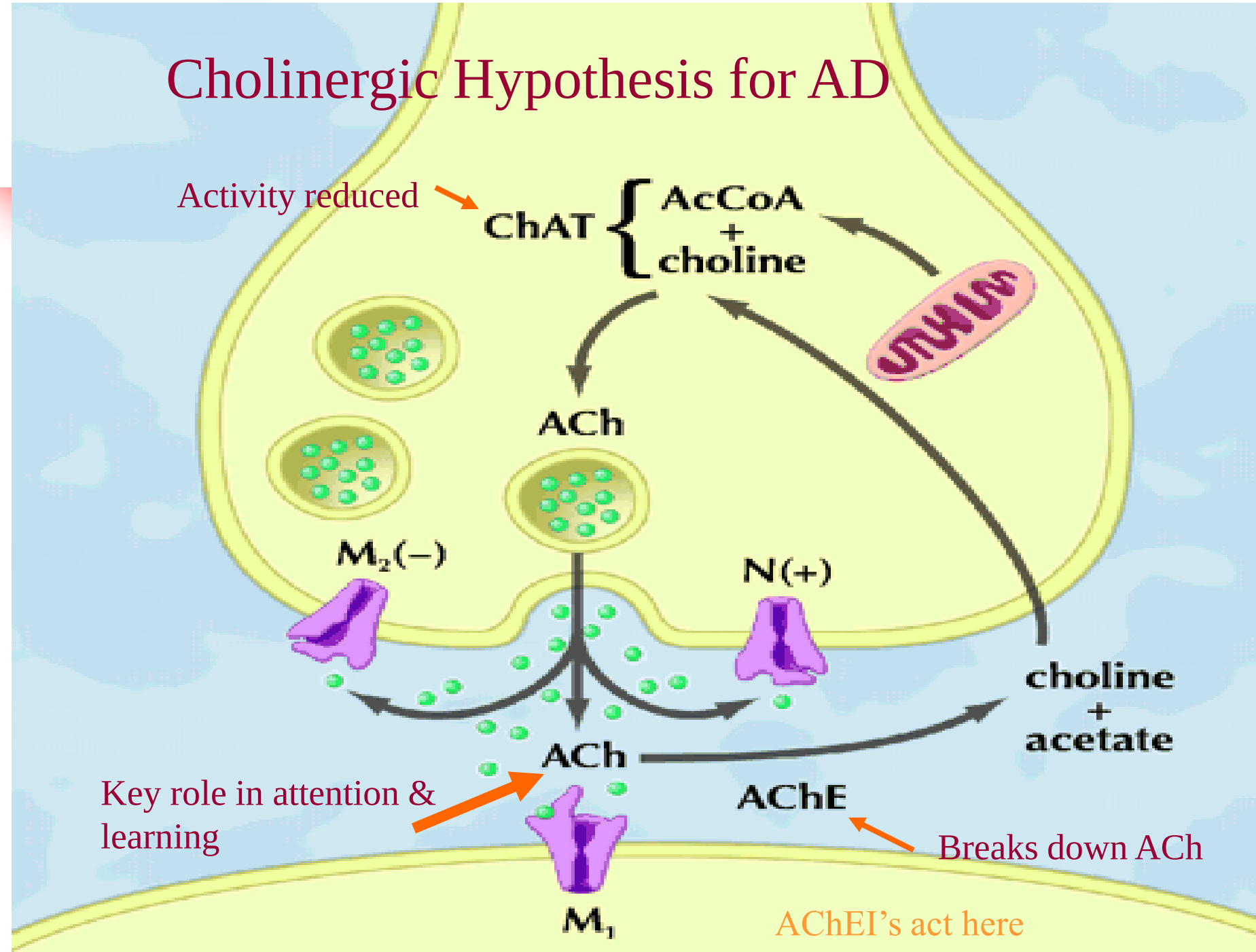
Overall mortality for the nursing home residents during the 18-month course of the study is shown. The residents' median age was 86 years, and the median duration of dementia was 6 years; 85.4% of residents were women.

Mitchell, M. et al. N Engl J Med 2009;361(16): 1529-38

Patient CF, aged 63, female

- Admitted with "Agitated dementia"; limited verbalization; CT scan: atrophy>expected for age
- PMH:
  - 2004 –Alzheimer's Disease age 58; MMSE 23/30
  - 1980 – Depression; hospital x 2 months
  - Hypertension
- SH: 2 children; worked as a secretary; stopped working in 2001 due to memory problems
- Treatment:
  - 2004 – Donepezil (Aricept)
  - 2004-06 – Galantamine (Reminyl)
  - 2006-09 – Memantine (Ebixa)

Cholinergic Hypothesis for AD



Cholinesterase inhibitors

- Prevent breakdown of acetylcholine in the brain
  - Chemical messenger needed for learning and memory
  - AChE levels are low in AD
- Three agents available for mild to moderate dementia
  - Donepezil (Aricept)
  - Rivastigmine (Exelon)
  - Galantamine (Reminyl)

Cholinesterase inhibitors

- Consistent benefits in RCT's on patients' cognition and global clinical state
  - Measured using 11 item cognitive section of AD Assessment Scale
  - Cognitive responder (1 additional person to achieve an improvement of 4 pts or more) NNT = 10
  - Global responder (minimal improvement on scale) NNT = 12
- Is this response clinically relevant?
- How long can benefit be expected to last?

Cholinesterase inhibitors adverse effects

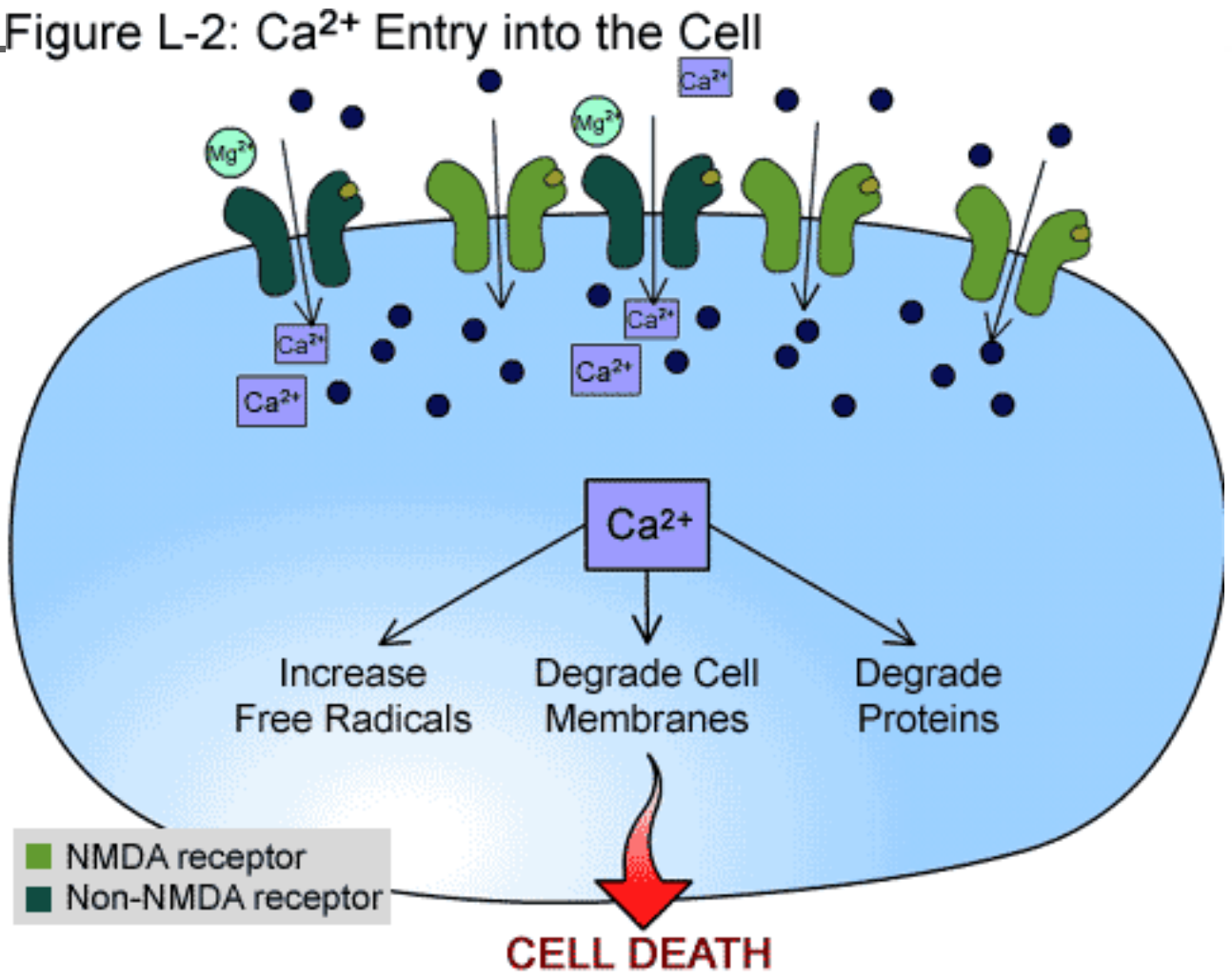
DRUG	Nausea	Vomiting	Headache	Insomnia
Donepezil (Aricept)	11%	__	10%	9%
Galantamine ER (Reminyl)	17%	7%	8%	___
Rivastigmine (Exelon) oral	37%	23%	15%	___

Syncope, Bradycardia, Pacemakers and Hip Fractures

- Cholinesterase inhibitor cohort vs. control cohort, mean age 80 yrs
- Syncope: 31.5 events/1000 person yrs
  - HR 1.76
- Bradycardia: 6.9 events/1000 person yrs
  - HR 1.69
- Pacemaker inserted: event rate = 6.9
  - HR 1.49
- Hip fracture: event rate = 22.4
  - HR 1.18

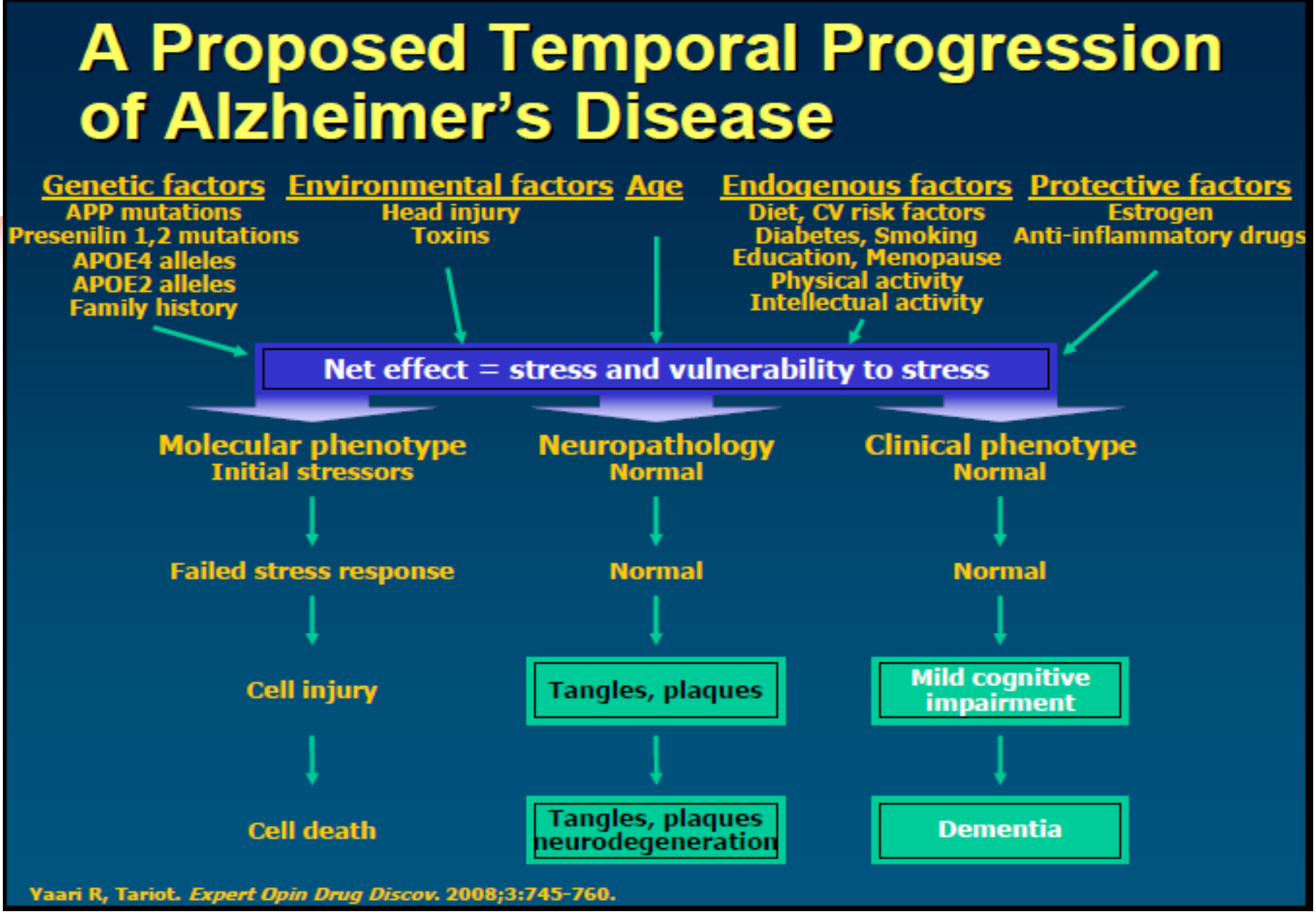
Arch Intern Med. 2009;169(9):867-873

Memantine: mechanism of action



Memantine (Ebixa)

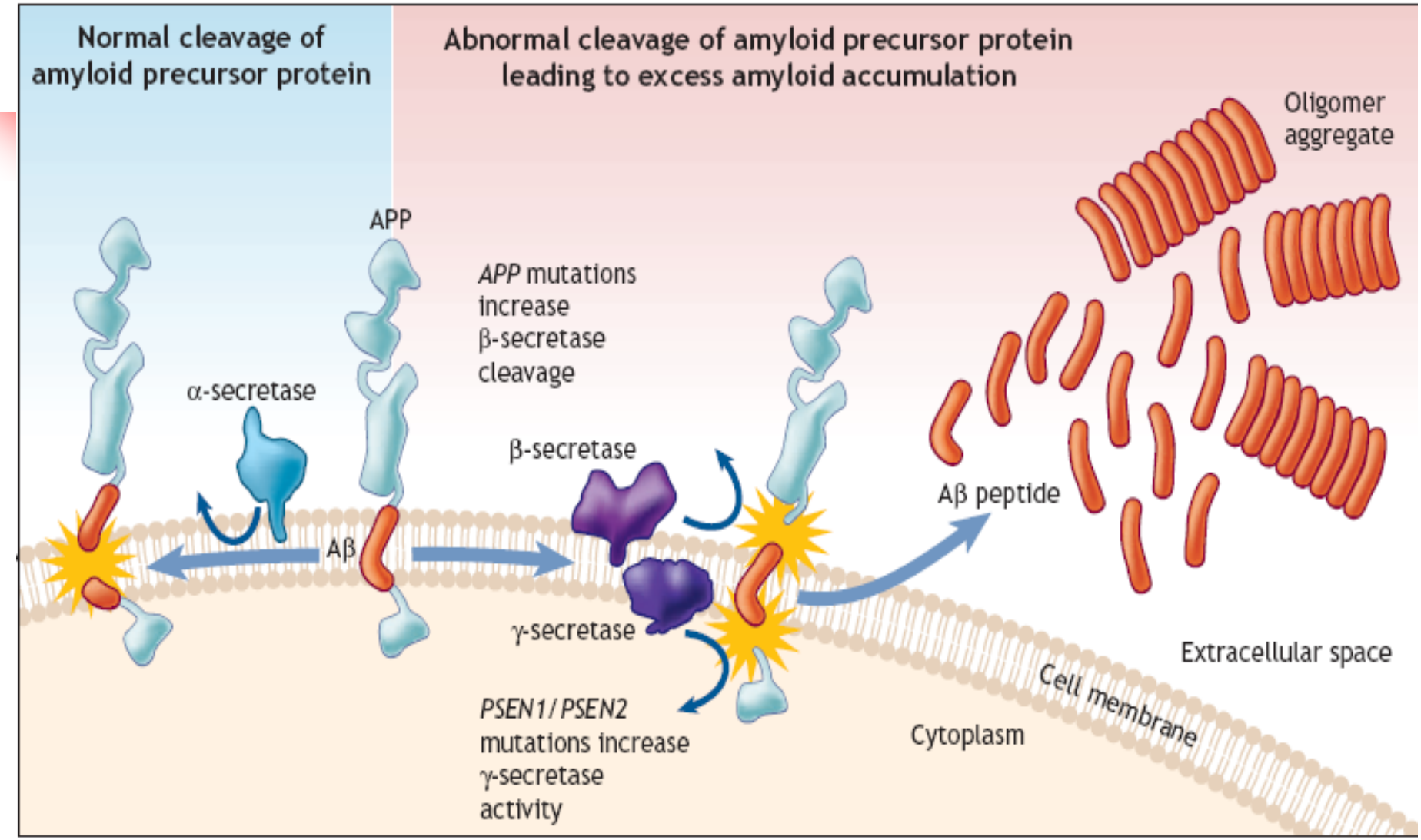
- NMDA receptor antagonist
  - Modulates glutamate concentrations and prevents harm to neurons; glutamate is crucial for learning and memory
- Approved for use in moderate to severe AD alone or with a cholinesterase inhibitor
- Recent data shows benefit in severe AD with language impairment and in Frontal Lobe dementia



Source: "Update on AD Research", P.Tariot, U. Arizona College of Medicine, @5th CCD, Toronto,2009

Factors we can not change

- Age – risk doubles with every 5 years after age 60
- Genetics – APP mutations, APOE-4 & APOE-2 alleles



Source: "Diagnosis and treatment of dementia: Risk assessment and primary prevention of Alzheimer disease", CMAJ 2008;178(5):548-56

Active Immunization

- Phase II clinical trial of active immunization with an aggregated beta-amyloid peptite
  - N = 372
  - Trial was terminated prematurely due to 6% of patients developing meningoencephalitis, like due to a pro-inflammatory T-cell response against the Aβ peptide. Similar results seen in other active vaccination Phase II trials
  - No clinical benefit shown in responders & non-responders to the vaccine

Passive Immunization

- Antibodies might be able to bind to Aβ and draw it out of the brain
- Wyeth has a phase III trial for "bapineuzumab", a monoclonal antibody to beta-amyloid
  - The phase II study overall results were negative, but the secondary analysis suggested positive effects and adequate safety, justifying phase III trials which are underway now
- Lilly has phase III trial for "LY206430", which targets beta-amyloid
  - Phase II trial showed safety/tolerability, and showed an increase in peripheral beta-amyloid after antibody infusion

Human Intravenous Immunoglobulin (IVIg)

- Currently available for treatment of other neurological disorders
  - Ex: Multiple Sclerosis – Tysabri (natalizumab)
- Treatments for AD contain anti-beta-amyloid antibodies
  - Other open-label & phase II studies have shown positive effects in reducing beta-amyloid in the CSF
  - Eli Lilly has started enrolling patients in April 2010 for 2 Phase III clinical trials using "solanezumab"
  - Baxter started an 18 month Phase III trial in September 2008 for "Gammagard liquid" (Kiovid)

Secretase Pathway

1. Beta-secretase inhibitor
   - Prior agents have failed
   - At least 1 promising agent approaching clinical trial (Schering-Plough)
2. Gamma-secretase inhibitor
   - Various agents have shown the desired biological effect
   - Eli Lilly has 2 phase III trials with "Semagacestat 140mg daily vs placebo x 21 months" – 1100 participants
   - "Tarenflurbil" (Flurizan™) failed to show benefit in phase III trials

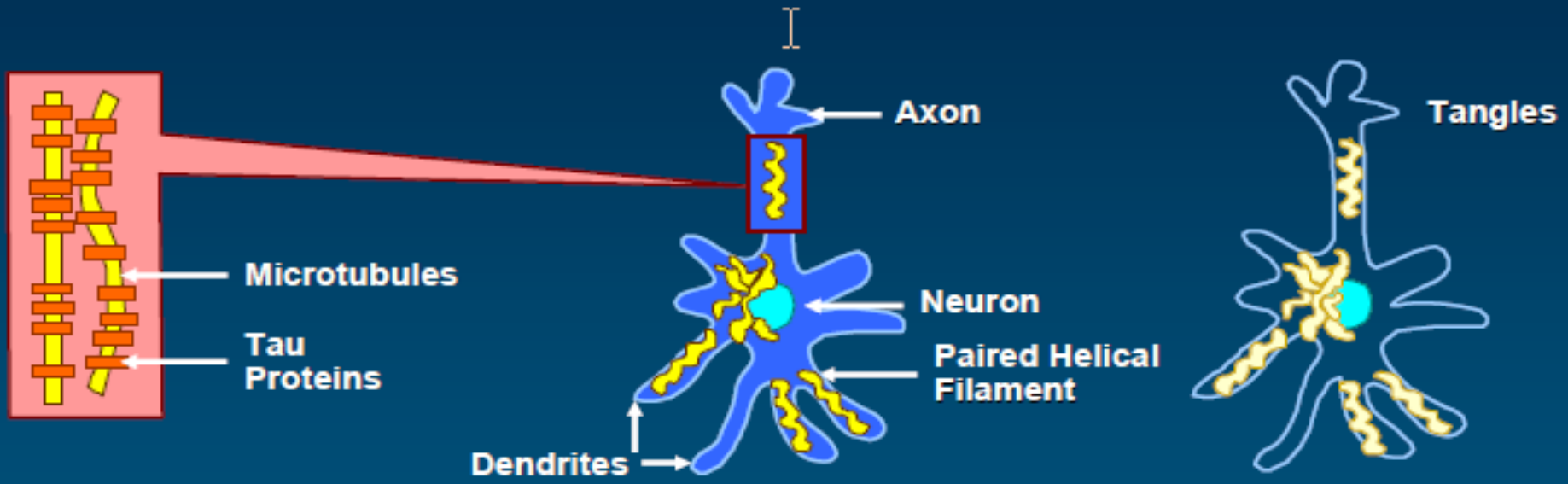
Anti Amyloid Therapy Conclusions

- Many medications and immunotherapies exist that can alter the processing of amyloid in the lab and in animal models
- They have shown at least some ability to alter blood and or spinal fluid measures of different types of amyloid in people with AD
- Effects on MRI, PET, other biomarkers in humans unclear/unknown
- Dose ranges not established in all cases
- Clinical significance of encouraging proof of concept biomarkers remain unknown
- This is a very active area of treatment research

Source: "Update on AD Research", P.Tariot, U. Arizona College of Medicine, @5th CCD, Toronto,2009

Theories of How Damage Occurs in AD

From Inside the Cell: Tangle Formation



Tau proteins, which normally stabilize microtubules in brain cells...

undergo abnormal chemical changes and assemble into spirals called paired helical filaments...

thus creating tangles that disrupt cell functions and lead to cell death.

Sources: Dr John Trojanowski and Dr Virginia M. Y. Lee. University of Pennsylvania Medical Center.

Source: "Update on AD Research", P.Tariot, U. Arizona College of Medicine, @5th CCD, Toronto,2009

Anti-tangle therapies

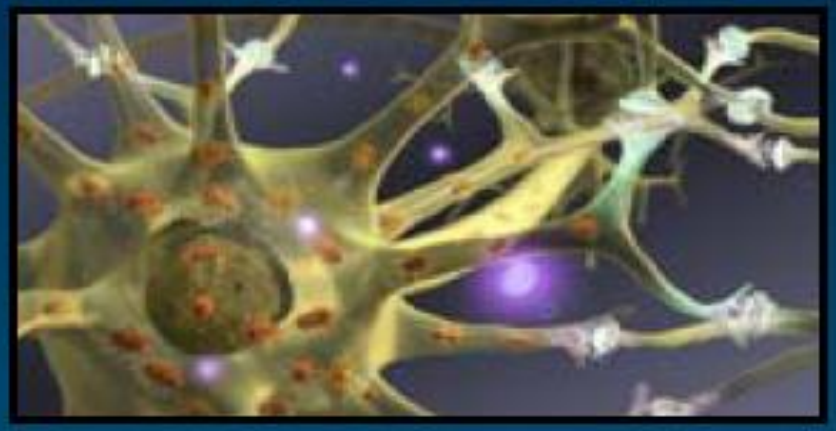
- Blocking tau-phosphorylation
  - Glycogen synthase kinase inhibitors
    - Astra Zeneca compound in early development
    - European trial completed, and no pharmacodynamic results were seen
    - Vaccination approaches for this theory are in early development

Inibiting tau aggregation

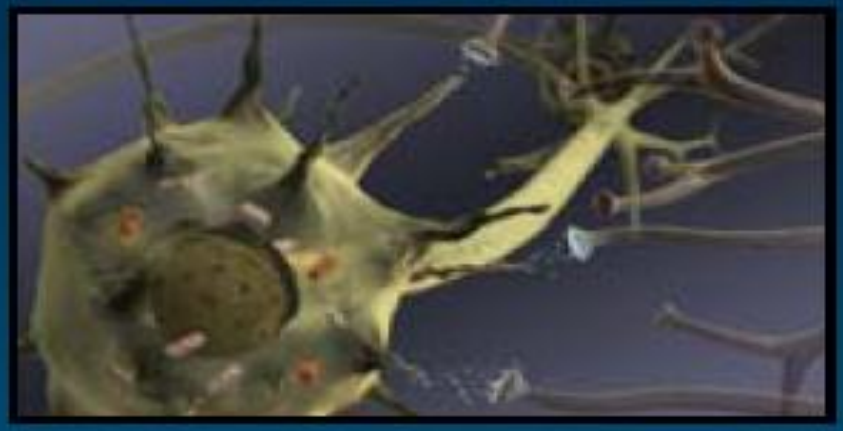
- Blocking the formation of tau oligomers and their conversion to paired helical filaments
- Results for “methylthioninium” (Rember™) in Phase II trials (2008) were positive, but no follow up trial has been done yet.

Mitochondria as a Target for AD

Healthy Neuron



Alzheimer's Disease Neuron



- β-amyloid can accumulate in the mitochondria resulting in decreased ATP production, increased oxidative stress, and apoptosis
- Other pathologic and neurodegenerative processes in AD ultimately result in mitochondrial dysfunction
- Improved mitochondrial function may promote neurite outgrowth and synaptogenesis, normalize calcium dysregulation, and inhibit apoptosis

Source: "Update on AD Research", P.Tariot, U. Arizona College of Medicine, @5th CCD, Toronto,2009

Dimebon (Latrepirdine)

- Old antihistamine used in Russia
- Weak inhibitor of cholinesterase & NMDA receptors. Inhibits neuronal cell death, potentially by mitochondrial-mediated inhibition of apoptosis
- CONNECTION study (phase III) – showed benefit vs placebo at 1 year
  - On March 3, 2010, Medivation announced that the Phase III study failed to demonstrate a statistically significant response compared to placebo in 2 measures of memory & cognitive function
- CONCERT study (phase III) – currently enrolling participants with mild-moderate Alzheimer's disease on Donepezil to evaluate Dimebon vs placebo.

Overview of other Experimental Therapies for Alzheimer's Disease

Name	Role in Alzheimer's Disease	Any Benefit??
Huperzine "natural" cholinesterase inhibitor derived from the Chinese herb *Huperzia serrata*	Same effects as current AChE's, but may also have antioxidant and neuroprotective properties	Some +/- results Phase 4 trials on-going in China Phase II trial in US was completed. Development of this drug is inactive.
Atomoxetine Norepinephrine-reuptake inihibtor	"stimulant"	Results pending - trial showed (-) primary outcomes, but (+) secondary outcomes
Varenicline (Champix)	Binds with nicotinic acetylcholine receptors, improving attention, learning & memory	Pfizer trial started March 2009 will evaluate effects on cognition, safety & tolerability in mild-moderate AD

Overview of other Experimental Therapies for Alzheimer's Disease

Name	Role in Alzheimer's Disease	Any Benefit??
H_3 (histamine)-recpetor antagonists found in the brain only (H_2-receptor antagonists ex: ranitidine are found in brain & periphery)	Histamine release in the brain triggers neurons to release acetylcholine	No positive results yet
Nicotinic α-7 receptor agonists Highly expressed in the brain, and limited in the periphery	Increase cholinergic neurotransmission, and have a better safety profile than observed with current therapies	On May 12, 2010 En Vivo announced the initiation of a Phase IIb trial. Recruitment has not yet started.
Antioxidants "Vitamin E"	Thought to prevent brain cell damage by destroying toxic free radicals	No (+) data, or pending treatment trials

Overview of other Experimental Therapies for Alzheimer's Disease

Name	Role in Alzheimer's Disease	Any Benefit??
Anti-inflammatories Ibuprofen/Naproxen	May aid in preventing or delaying the onset of AD by decreasing inflammation in the brain	Phase III trials on-going
Hormonal therapies Estrogen	Has both antioxidant & anti-inflammatory effects and enhances the growth of neurons that release acetylcholine	Discouraging WHIMS results No definite conclusions can be made based on current evidence.
Cholesterol-lowering agents "statins"	- plaque busters; act on β-secretase & α-secretase activity	Retrospective studies showed an association b/w taking statins & ↓ prevalence of AD ADCS & Phizer trials (-)

Overview of other Experimental Therapies for Alzheimer's Disease

Name	Role in Alzheimer's Disease	Any Benefit??
Insulin sensitizing agents *Rosiglitazone*	Diet-induced peripheral insulin resistance has been shown to ↑ γ-secretase activity & ↓ insulin-degrading enzyme activity. These combined changes result in ↑ β-amyloid levels and amyloid plaque burden in the brain.	Smaller trials showed (+) benefit 3 Phase III trials terminated early due to (-) preliminary results from completed trial in Sept 2009
Calcium-channel antagonist *Nimodipine*	Neuronal Ca+ levels are regulated by specific calcium proteins channels. Abnormal regulation of these channels is believed to be an early step in AD, 1st impairing the pathways required for memory and other cognitive functions, and eventually causing cell death	Phase II testing complete Future development incertain

Overview of other Experimental Therapies for Alzheimer's Disease

Name	Role in Alzheimer's Disease	Any Benefit??
Omega-3 fatty acids	Patient's with AD have significantly lower DHA levels compared to control subjects, and serum DHA levels are progressively reduced with severity of clinical dementia	Some benefit for patients with cognitive decline (not AD or MCI) 18-month study did not meet primary endpoints, but secondary analysis of data by ApoE4 genotype showed significant effects on MMSE scores & ADAS-Cog scores.
Ginkgo Biloba "herbal"	Improve cognitive capacities, possibly via antioxidant or antiplatelet actions	RCT demonstrated modest improvements

Factors we CAN change:

- **CVA risk factors**
  - **Blood pressure – target SBP ≤ 140mmHg**
  - **Cholesterol levels –same targest as in stoke**
  - **Glucose control in diabetes**
- **Lifestyle factors**
  - **Diet** – mid-life adiposity ↑ risk of dementia independent of diabetes
  - **Physical activity**
  - **Intellectual activity** – brain stimulating activities
  - **Social engagement**
  - **Moderate alcohol intake**
  - **Avoid tobacco use**
  - **Avoid head injuries**

Nutrition

- "Nutrient" vs "Diet"
  - Nutrient deficiencies rarely exist in isolation
  - We still 'promote' nutrient supplementation instead of diet changes!
    - Example: taking fish oils caps vs eating fish
- New research looking at "Diet"
  - Mediterranean diet – high in fruits/veggies + grains, olive/canola oil as 1 fat source, fish intake weekly, moderate amout of meat **(once per month)**….. And exercise!!

Source: "Nutrition", Dr. C Greenwood, U. of Toronto Faculty of Medicine, @5th CCD, Toronto,2009

Physical Exercise

- CAN help in preventing age-related cognitive decline in:

1. Healthy older adults
2. Mild Cognitive Impairment + dementia
3. Frail older persons (10-20% of persons 80+)
   - Studies show an increase in physical capacity, improvement in cognitive function, improved quality of life (psychological well-being), help maintain cognitive function (leisure activities)
   - Benefits of physical exercise on cognitive and QoL can be observed in frail older adults after only 3 months!

Source: "Physical Exercise", Dr L. Bherer, U du Quebec a Montreal, @5th CCD, Toronto,2009

Intellectual Activity

- Cognitive **stimulation** – involvement in activities to non-specifically increase cognitive and social functioning
  - ex: discussions, supervised leisure activities, list memorization, reminiscence, video games, crossword puzzles, board games, card games
- Cognitive **training** – theoretically motivated; teaching strategies and skills in a structured and standardized fashion
  - ex: mneumotechnics (memory programs)
- Cognitive **rehabilitation** – centered on specific activities of daily life with an individualized approach
  - ex: learning the name of a caregiver

Source: "Cognitive Training", Dr S Belleville, Universite de Montreal, Psychology department, @5th CCD, Toronto,2009

Social Engagement

- **What is social activity?**
  - Any interaction with people (or animals) doing specific activities (leisure, work, domestic) b/w or among people (co-workers, friends, family)
- **Social Networks**
  - Extensive social network
    - Being married and living with someone
    - Having children and having daily to weekly satisfying contacts with them
    - Having relatives and/or friends and having daily to weekly satisfying contacts with them
  - Moderate social network
    - Having any **two** of the above 3 conditions
  - Limited social network
    - Having any **one** of above 3 conditions
  - Poor social network: being single and living alone; no children and no close social ties

Source: "Social Networks", Dr J Kaye,Oregon Health & Science University, Department Neurology, @5th CCD, Toronto,2009

Patient, CF, age 63, female

- Experienced increased agitation, anguished crying out, hallucinations
- High dose Olanzapine + Sertraline = akathisia
- Medication adjustments, wheelchair, complete feed, continues to attempt verbal response
- Transferred to nursing home

Summary

- Early diagnosis & education is important for many reasons
  - Early access to new treatments in development
  - Patient & family can prepare for disease progression (advanced directives)
- Current treatments provide some benefit, but this must be weighed against potential adverse reactions
- New treatments are moving forward into Phase III clinical trial, which is promising
- There is good evidence to support non-pharmacologic options for prevention and management