

2010 AD: Developments in Alzheimer's Disease and Other Dementias

Emily Trittschuh, PhD

Geriatrics Research Education and Clinical Center (GRECC)
VA Puget Sound Health Care System

Dept of Psychiatry and Behavioral Sciences
University of Washington

emily.trittschuh@va.gov

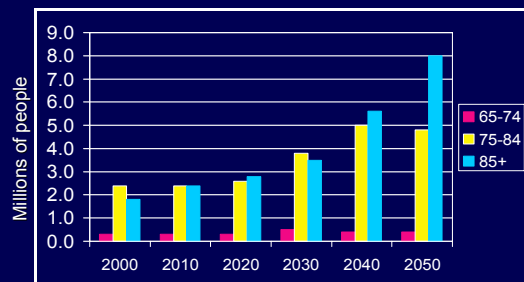


Alzheimer's Concepts and Tx

- Why is Alzheimer's disease an economic problem?
- Defining Alzheimer's disease
- Diagnosing Alzheimer's disease
- Discriminating between various dementias
- What are the current treatments for AD?
- What are the new directions of research?



Prevalence of AD in the US



Hebert, et al, 2003, Archives of Neurology

The U.S. Epidemic

- Older Americans represent ~12 % of the population.
 - 26% percent of physician office visits
 - A third of all hospital stays and of all prescriptions
 - Almost 40 % of all emergency medical responses
 - 90 % of nursing home residents
- In 2011, the first baby boomers will reach their 65th birthdays.
 - By 2029, all baby boomers will be at least 65 years old.
 - This group will join the rest of older adults to total an estimated 70 million people aged 65 and older.

*As reported by the Alzheimer's Association in 2010



The Costs – \$100 billion annually



- The average lifetime care cost for someone with AD is \$174k
- Yearly cost depends on the stage of the disease.
 - \$18,400 for someone with mild symptoms
 - \$30,100 for moderate symptoms
 - \$36,132 for severe symptoms.
- AD costs business \$24.6 billion in health care
- 7/10 people with AD live at home;
 - 75% of costs are absorbed by the family.
 - The remaining 25% of care costs cost an average \$19,000 a year
- \$42,000 is the average cost of a nursing home for 1 year; closer to \$70,000 in urban areas

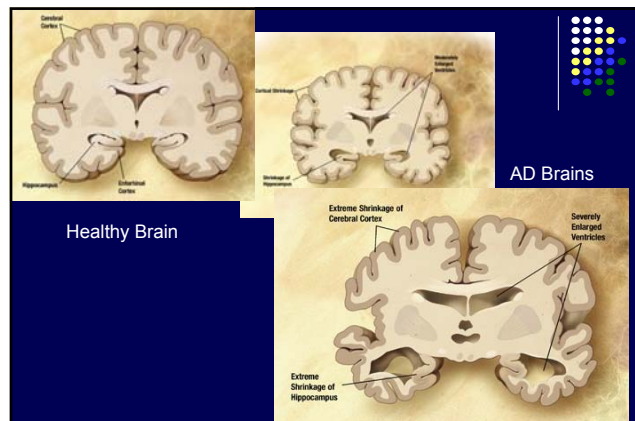
*from 2006 reports

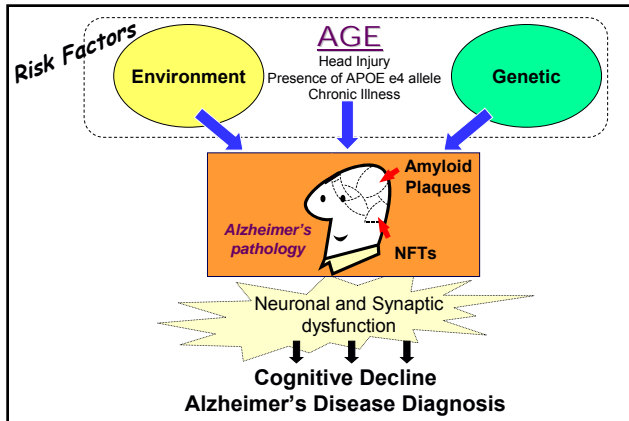
Alzheimer's Concepts and Tx

- Why is Alzheimer's disease an economic problem?
- Defining Alzheimer's disease
- Diagnosing Alzheimer's disease
- Discriminating between various dementias
- What are the current treatments for AD?
- What are the new directions of research?

Timeline History of AD - early

- **1901-1906** Dr. Alzheimer observes 51 year old female, Auguste D., of Frankfurt, Germany
 - cluster of symptoms including: – Aphasia – Disorientation – Unpredictable behavior – Paranoia – Auditory hallucinations – Pronounced psychosocial impairment
- **1906** Dr. Alzheimer published histological changes associated with AD
 -  **Amyloid plaques**
- aggregated beta-amyloid
 -  **Neurofibrillary tangles**
- hyperphosphorylated tau
- **1910** Emil Kraepelin names "Alzheimer's Disease"
1910-1960s AD remains little known disease





Genetics of Alzheimer's disease

- Only one consistent association for sporadic AD
 - E4 allele of APOE (gene found on ch19)
 - Review: Betram, et al., Nature Genetics, 39(1), January 2007
- Early-onset familial AD – rare autosomal dominant mutations - <5% of all cases
 - APP gene is mapped to chromosome 21
 - Trisomy 21 – Down Syndrome and AD by age 30
 - Major disease locus on ch14
 - Presenilin 1
 - Presenilin 2 – more recently found on ch1
 - Tau gene (FTD and associated tauopathies) on ch17
 - Goedert, et al., Science, 314, 777, 2006

Alzheimer's Concepts and Tx

- Why is Alzheimer's disease an economic problem?
- Defining Alzheimer's disease
- Diagnosing Alzheimer's disease
- Discriminating between various dementias
- What are the current treatments for AD?
- What are the new directions of research?

Definite Alzheimer's Disease

- Examination of brain tissue
 - Amyloid plaques
 - Neurofibrillary tangles
- Present in brain in a certain density & distribution



NINCDS-ADRDA Criteria from 1984 consensus group

Probable Alzheimer's Disease

- Dementia established by clinical and neuropsychological examination.
 - Explicit memory impairment plus at least 1 other area of dysfunction.
 - Activities of daily living have been affected.
- Insidious onset and progressive course.
- Onset between the ages of 40 and 90 years.
- Other diseases capable of producing a dementia syndrome have been ruled out.

NINCDS-ADRDA Criteria from 1984 consensus group

Criteria - Continued

- **Possible AD:** There is a dementia syndrome with an atypical onset, presentation or progression; and without a known etiology; but no co-morbid diseases capable of producing dementia are believed to be in the origin of it.
- **Unlikely AD:** The patient presents a dementia syndrome with a sudden onset, focal neurologic signs, or seizures or gait disturbance early in the course of the illness.

NINCDS-ADRDA Criteria from 1984 consensus group

DSM for Dementia Diagnosis

- DSM IV uses the diagnostic category: Delirium, Dementia, Amnestic, and Other Cognitive Disorders
 - Problems with the current DSM criteria
- DSM V - www.dsm5.org/ProposedRevisions/
- New diagnostic category would be Delirium, Major Neurocognitive Disorder and Minor Neurocognitive Disorder
- Major Neurocognitive Disorder - handouts
- not to be released until May 2013

How is Dementia Diagnosed?

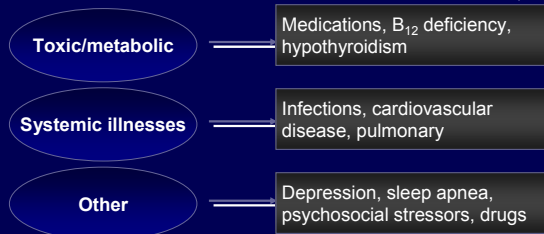
- Minimum work-up includes:
 - History and physical examination
 - Neurological examination
 - Mental status testing
- Recommended work-up includes:
 - Brain CT or MRI
 - Neuropsychological examination
 - Basic laboratory panel
 - Psychiatric consultation- if depression suspected

BIOMARKERS BUZZ



Causes that Mimic Dementia

(*but are treatable)



*Treatment may improve, but not fully reverse, symptoms

Neuropsychology of AD

- Tests
 - Consider age of subject and overall health/energy
 - Consider adjusting measures administered based on referral question (e.g., first diagnosis vs. current function)
- Normative populations
 - Limited normative information for 90+
 - Non-native English speakers
 - Ethnicity/Cultural differences
- Premorbid estimates
 - Individualized benchmark

Biomarkers for Diagnosis of AD

- Beta amyloid imaging
- MRI – volumetrics
 - Cortical thickness mapping/volume of medial temporal lobe
 - Ventricular volume as evidence for atrophy
- CSF key markers– β -amyloid protein 1-42 ($a\beta_{1-42}$), total CSF tau, P-Tau

Diagnosis-Independent Alzheimer Disease Biomarker
Signature in Cognitively Normal Elderly People
De Meyer, Shapiro, Vanderstichele, Vanmechelen, Engelborghs, De Deyn, Coart, Hansson, Minthon, Zetterberg, Blennow, Shaw, Trojanowski; for the Alzheimer's Disease Neuroimaging Initiative
Archives of Neurology, 67, August 2010

Mild Cognitive Impairment

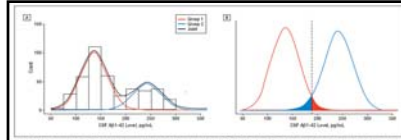
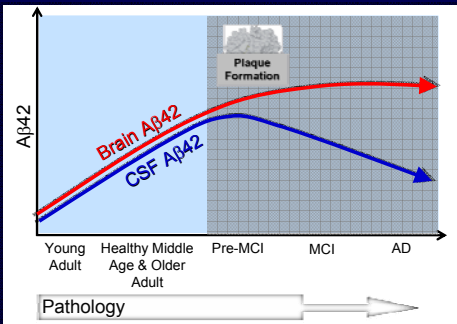
(Petersen et al., 1999, 2001)

- Objectively measured deficits in memory and/or other thinking abilities
- Normal ADLs
- Not demented
- Subjective memory complaint

** Conversion to dementia is significantly higher in people with MCI

MCI 12 - 15% per year
Normal controls 1 - 2% per year

Model of A β Changes - Health to AD



Used Mixture Model classification to determine an AD signature

Figure 3. Mixture model identification for combined fluid-derived p-amyloid protein 1-42 (CSF A β 1-42). Results are presented as a histogram of observed counts for the combined population and the individual population components.

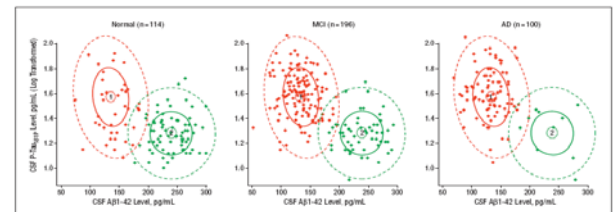


Figure 4. A combined cerebrospinal fluid-derived p-amyloid protein 1-42 (CSF A β 1-42)/CSF phosphorylated tau₄₀₄ (CSF P-Tau₄₀₄) mixture model applied to the subject groups. Describes of each signature are represented with confidence ellipses, and signature membership of the subject based on the mixture is indicated with the corresponding color (signature 1 is the Alzheimer disease [AD] signature [red]; signature 2 is the healthy signature [green]). MCI indicates mild cognitive impairment.

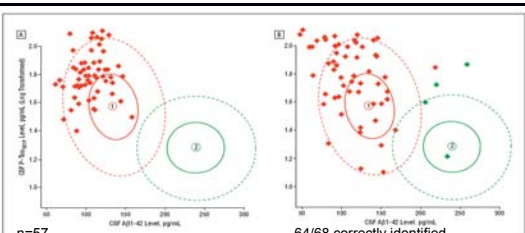


Figure 5. Validation of the combined cerebrospinal fluid-derived p-amyloid protein 1-42 (CSF A β 1-42)/CSF phosphorylated tau₄₀₄ (CSF P-Tau₄₀₄) mixture model in 2 data sets. A. Patients with mild cognitive impairment who developed Alzheimer disease within 5 years after the CSF sample. B. Patients with idiopathic-onset Alzheimer disease with memory loss less than 1 year between CSF sample and autopsy (n=68). * Signature 1 is the Alzheimer disease signature (red); signature 2 is the healthy signature (green).

- 100% predictive in people who already had a memory problem
- Hopefully this will help researchers and drug companies build better studies
- Not ready for primetime as a clinical diagnostic tool – aka “I’m not out of a job yet”

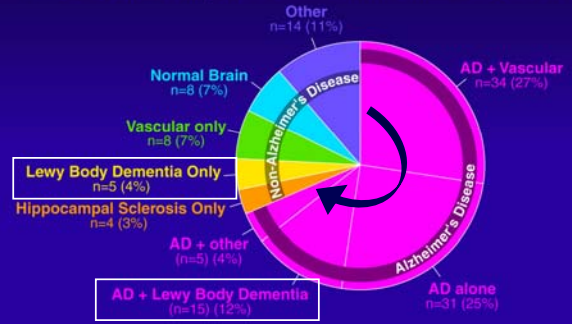
Alzheimer’s Concepts and Tx

- Why is Alzheimer’s disease an economic problem?
- Defining Alzheimer’s disease
- Diagnosing Alzheimer’s disease
- Discriminating between various dementias
- What are the current treatments for AD?
- What are the new directions of research?

Is it always Alzheimer's disease?



Neuropathological Diagnosis in 124 Community-based Incident Dementia Cases



Consensus Criteria for Dementia with Lewy Bodies

1. Meets criteria for Dementia
2. Core features (2 = "probable", 1 = "possible")
 - a. fluctuating cognition, attention, alertness
 - b. recurrent visual hallucinations
 - c. spontaneous features of parkinsonism
3. Suggestive features (plus one core = "probable" DLB)
 - a. REM sleep behavior disorder
 - b. severe neuroleptic sensitivity
 - c. low dopamine transporter uptake (PET/SPECT)
4. One year rule for PDD vs. DLB

McKeith et al. *Neurology* 65:1863-72, 2005.

LBD - Associated Features

- Repeated falls
- Syncopal episodes
- Neuroleptic sensitivity
- Neuropsychiatric symptoms
- Prominent impairments in attention, executive functions and visuospatial abilities
- Sleep disorders
 - e.g., REM sleep behavior disorder

Neuropsychiatric symptoms in LBD

Symptom	Frequency	Comments
Visual hallucinations	42-84%	Usually well-formed
Delusions	50-70%	Often paranoid component
Auditory hallucinations	up to 50%	Usually accompany visual hallucinations
Delusional misidentification	up to 50%	Misidentification of common objects, such as mirror images and television images
Depression	20-50%	Similar to frequency of depression in AD

Reviewed in Ericksen and Tsuang, 2007

Cognitive Phenotype: AD vs LBD

	Alzheimer's	LB Dementia
Attention	++	++++
Memory	++++	++
Executive	+++	++++
Visuospatial	+++	++++
Language	++++	+

Frontotemporal Dementia Core Features

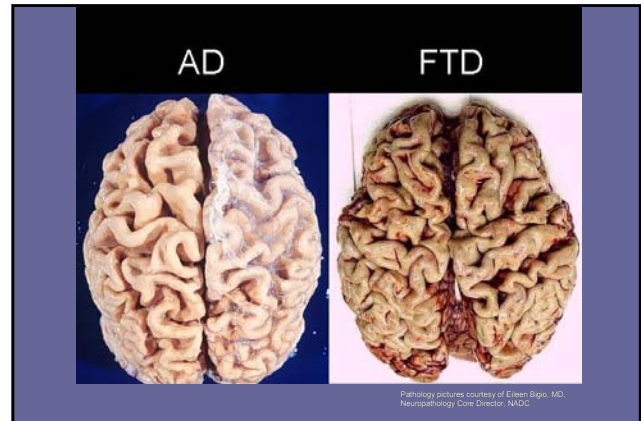
- Early decline in comportment (social interpersonal conduct):
 - Incongruent with patient's premorbid personality
 - Decline in manners, social graces, decorum
 - Disinhibited verbal, physical, and/or sexual behavior
 - Passivity, inertia, abulia
- Early emotional blunting
- Early loss of insight

FTD - Associated Features

- Absence of severe amnesia, aphasia or visuospatial disorder
- Impairments on executive function tasks
 - Poor set shifting
 - Inability to inhibit overlearned responses
 - Poor organization and temporal sequencing
- May demonstrate *secondary* impairments on memory, language or visuospatial tests as the result of attentional and executive dysfunction.

FTD - Associated Features

- Onset is typically before age 65
- Family history of similar condition in approximately 50% of cases
- Motor neuron disease
 - Evident in a small group of patients



Alzheimer's Concepts and Tx

- Why is Alzheimer's disease an economic problem?
- Defining Alzheimer's disease
- Diagnosing Alzheimer's disease
- Discriminating between various dementias
- What are the current treatments for AD?
- What are the new directions of research?

Do we have a cure or tx for AD?

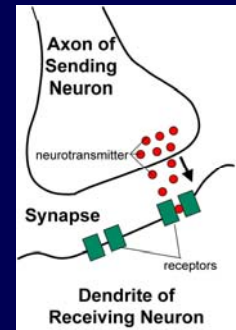
- No cure and the cause of AD is not understood
- Effective intervention = improve functional status to a degree discernable to caregivers or health care providers
- In the case of a progressive disorder, **"improvement" = slower decline**

Current FDA-Approved Medications

Acetylcholinesterase Inhibitors		
<i>tacrine</i>	Cognex®	hepatotoxic
donepezil	Aricept®	1 month
galantamine	Razadyne®	4 months
rivastigmine	Exelon®	4 months; patch
NMDA receptor antagonist		
memantine	Namenda®	1 month; approved for mod-severe AD
Adjunct Therapies (off label)		
Antidepressants	SSRIs, mirtazapine	
Antipsychotics	risperidone, quetiapine	

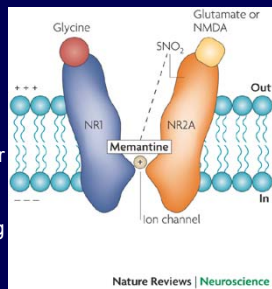
Acetylcholinesterase Inhibitor

- Acetylcholine is a neurotransmitter – part of cholinergic system of the brain
- Damage to the cholinergic (acetylcholine-producing) system in the brain has been shown to be plausibly associated with the memory deficits associated with Alzheimer's disease



Memantine – NMDA receptor antagonist

- NMDA receptor responds to glutamate (the main excitatory neurotransmitter in the central nervous system)
- NMDA receptors have an important physiological role in learning and memory, but receptor overactivation owing to increased glutamate release leads to excessive calcium entry, triggering neuronal death, a phenomenon termed 'excitotoxicity'



- 1993 Cognex is first FDA approved drug to treat AD
- 1994 Possible effect of estrogen on AD is postulated
- 1996 Aricept FDA approved
- 1997 Effect of antioxidants on AD studied
- 1999 Genetic mutations linked to programmed cell death of neurons
 - Development of techniques leading towards direct genetic manipulation for treatment of AD
 - First anti-AD vaccine tested
- 2000 Exelon FDA approved to treat AD
 - Brain imaging used to study AD
- 2001 Razadyne (previously Reminyl®) FDA approved
- 2002 Clinical trial of anti-Alzheimer's disease vaccine conducted
- 2003 Namenda FDA approved
- 2004 President Reagan dies of AD
 - Diabetes linked with increased risk of Alzheimer's

Alzheimer's Concepts and Tx

- Why is Alzheimer's disease an economic problem?
- Defining Alzheimer's disease
- Diagnosing Alzheimer's disease
- Discriminating between various dementias
- What are the current treatments for AD?
- What are the new directions of research?

But first, what are the risk factors for AD?

*Most significant
risk factor for
AD is . . .*

AGE



Risk Factors that can be Managed or Avoided

Medical Conditions

- High Blood Pressure
- High Cholesterol
- Type II Diabetes

Behavioral Factors

- Nutrition/Diet
- Alcohol / Tobacco
- Exercise
- Stress
- Socialization

High Blood Pressure



- HBP and other stroke risk factors can damage blood vessels in the brain and reduce the oxygen supply.
- Damage may disrupt nerve cell circuits that are thought to be important to decision-making, memory, and verbal skills.
- According to observational studies, antihypertensive treatment is related to a reduced risk of Alzheimer's disease (AD).

Research

- Valsartan, a hypertension drug, was administered to mice who were tested for spatial learning
- Those mice with a genetic risk for AD showed improved memory
- Wang, et al. J Clin Invest. 2007 Nov;117(11):3393-402

High Cholesterol



- High levels of blood cholesterol are a known risk factor for heart disease.
- Basic research in laboratories as well as population and animal studies have suggested there may also be a connection between high levels of blood cholesterol and development of AD.
- Human and animal studies have raised the possibility that **statins**, the most commonly prescribed cholesterol lowering drugs, may reduce the risk of dementia.
- Other studies, though, have found no association between statins and dementia risk. Thus, it is not clear at this time whether statins affect the onset or progression of AD.

<http://www.nia.nih.gov/Alzheimers/Publications/ADPrevented>

Another Heart Disease risk factor



- High levels of homocysteine are known to increase heart disease risk.
- A high level of the amino acid homocysteine is associated with an increased risk of developing AD.
 - NIA studies in mice have shown that high levels of this amino acid can make neurons stop working and die.
- Blood levels of homocysteine can be reduced by increasing intake of folic acid and vitamins B6 and B12.
 - An NIA-funded clinical trial is currently studying whether reducing homocysteine levels with folic acid and vitamin B6 and B12 supplements will slow the rate of cognitive decline in older adults with AD pxs

Type II Diabetes and Risks of Alzheimer's Disease



Older adults (>55 yrs) with diabetes have a 65% increased risk of developing Alzheimer's disease (compared to those without diabetes)



Adults with diabetes have lower scores on cognitive tests

Bennett, et al. Religious Orders Study. *Archives of Neurology*, 2004

- ✓ Some additional shared characteristics: genetic predisposition and deposits of two different kinds of damaging amyloid protein (in the brain for AD and in the pancreas for diabetes).
- ✓ Abnormal glucose (a type of sugar) regulation, a key element of diabetes, also has been associated with development of AD.

“Pre” Diabetes? – Insulin Resistance

- Insulin plays a role in normal brain function
- Disrupting insulin leads to cognitive impairment, accelerated brain aging, and dementia
- Insulin resistance: a new epidemic with disastrous consequences?
- Treating insulin resistance may prevent or delay age-related cognitive decline and neurodegenerative disease
- **SNIFF study – intranasal insulin administration**

ICAD 2010 Presentation: S Craft, et al.

More Risk Factor Facts

- Individuals with Alzheimer's disease who also have diabetes and/or hypertension may die sooner than those with Alzheimer's who do not have these additional conditions.
- A study of 323 people found that after a diagnosis of Alzheimer's disease, those with diabetes were twice as likely to die sooner than those who did not have diabetes.
- Those with hypertension were 2.5 times more likely to die sooner than those with normal blood pressure.
- Pre-AD dx - higher total cholesterol and LDL-C concentrations and history of diabetes were associated with faster cognitive decline in patients with incident AD.

From the Taub Institute for the Research on Alzheimer's Disease and the Aging Brain and the Cognitive Neuroscience Division of the Gertrude H. Sergievsky Center at Columbia University Medical Center

Alzheimer's Concepts and Tx



- Why is Alzheimer's disease an economic problem?
- Defining Alzheimer's disease
- Diagnosing Alzheimer's disease
- Discriminating between various dementias
- What are the current treatments for AD?
- What are the new directions of research?

Alzheimer's Prevention =

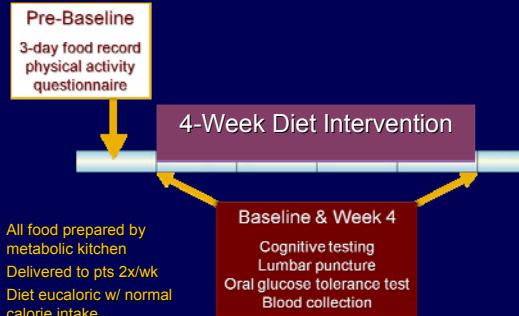
HEALTHY
Aging

Healthy Eating, Physical Exercise, Socialization,
and Cognitive Activity

Physical Activity

- Animals studies show that BOTH physical and mental function improve with aerobic fitness.
- In humans, improvements in fitness were associated with increased functioning in certain regions of the brain. The walkers were able to pay attention better and focus more clearly on goals while disregarding unimportant information.
 - In another study of nearly 6,000 healthy women 65 years old+ over a period of up to 8 years, investigators found that the women who were more physically active were less likely to experience a decline in their mental function.
- How could this work?
 - Physical activity may improve blood flow to the brain so that it responds better to a task.
 - It may activate cellular mechanisms that improve brain function.
 - We still don't know whether physical activity can actually prevent cognitive decline or postpone the development of AD, especially in people with a high genetic risk.

MEAL - Study Design



ICAD 2010 Presentation: Carter, et al. SCraft presenter

Diet Composition

• HIGH Diet (HSF/HGI)

- 45% Fat, 25% Saturated Fat
- 35-40% HGI Carbohydrate
- 15-20% Protein



• LOW Diet (LSF/LGI)

- 25% Fat, <7% Saturated Fat
- 55-60% LGI Carbohydrate
- 15-20% Protein



MEAL - Summary of Results

- Diet intervention successfully modulated insulin sensitivity & lipids
- LOW diet improved CSF biomarker profile & delayed memory for normal & MCI groups
- For normal adults, HIGH diet moved CSF biomarkers in pathologic direction:
 - Increased CSF A β 42
 - Reduced CSF insulin
- Short term HIGH diet did not further exacerbate AD biomarker abnormalities or cognitive symptoms

ICAD 2010 Presentation: Carter, et al. SCraft presenter

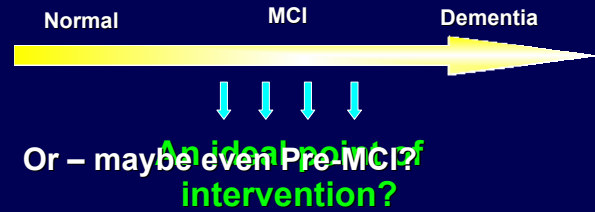
Implications

- Diet may be powerful environmental modulator of AD risk
- Dramatic & opposite effects on CSF A β levels for normal & MCI groups indicates:
 - Important role for dietary regulation of CNS A β in humans
 - Stage of pathology important for interpretation of CSF biomarker changes
- Dietary strategies may hold promise for AD primary and secondary prevention efforts

Other ideas

- Anti-inflammatory Medications – NSAIDs
 - Research has not supported the use of these for prevention/tx; some suggestion that timing may play a factor
- Antioxidants and Free Radicals
 - Vitamin E does not seem to slow progression – timing?
 - Another Phase 3 trial is ongoing
- Estrogen Replacement Therapy
 - Not supported for prevention thus far – again, could timing be an issue?
 - SERMs (selective estrogen-receptor modulators)

Mild Cognitive Impairment



Mild Cognitive Impairment

(Petersen et al., 1999, 2001)

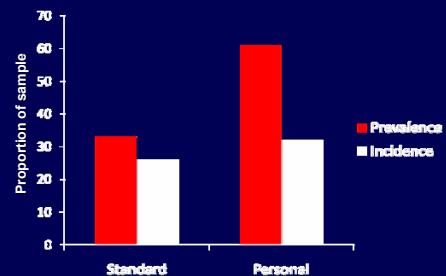
- Objectively measured deficits in memory and/or other thinking abilities
- Normal ADLs
- Not demented
- Subjective memory complaint

** Conversion to dementia is significantly higher in people with MCI

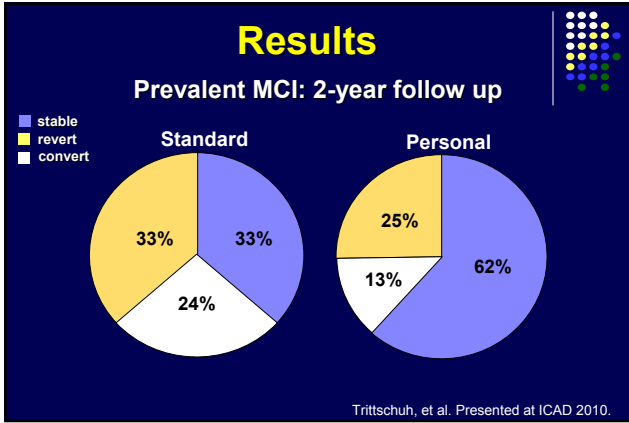
MCI 12 - 15% per year
Normal controls 1 - 2% per year

Results – MCI-epi study

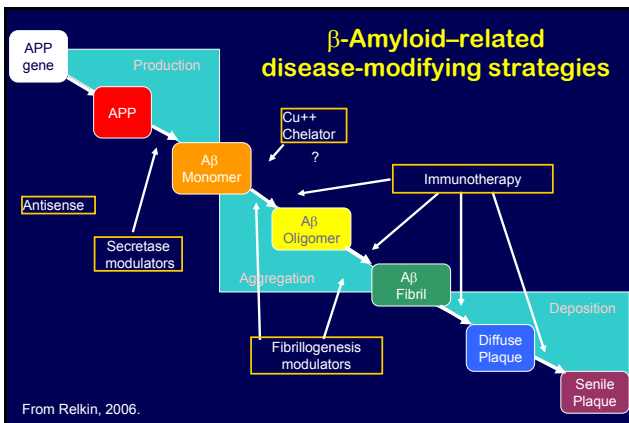
Prevalence and 2-year Incidence – n=137



Trittschuh, et al. Presented at ICAD 2010.



- ## Categories for new Therapies
- Drugs/nutraceuticals - (based on epidemiologic observations), e.g. resveratrol, alpha-tocopheral)
 - Neurotransmitter-based therapies - e.g., galantamine, namenda
 - Glial modulating drugs – e.g., TNF alpha antagonists
 - Neuroprotective drugs – e.g., mitochondrial stabilizers (Dimebon/latrepirdine)
 - **Amyloid modulating drugs**
 - Tau modulating drugs – anti-tangle meds, microtubule stabilizers (e.g., rember)



- ## Anti-amyloid summary
- 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, spinal fluid, PiB, and pathological measures of different types of amyloid in normals and/or people with AD
 - Effects on MRI, FDG PET, other biomarkers in humans unclear/unknown
 - Dose ranges not established in all cases
 - There is encouraging proof of concept but the clinical significance remains unknown

Drugs in the pipeline:

<http://www.alzforum.org/dis/tre/drc/default.asp>

- **Dimebon** – recently halted in Phase 3 trials
 - Early results did suggest stability for ~18 months
 - More trials planned
- **Flurizan** - flopped in Phase 3 trials
- **Rember** – Could not find info on its current status; an early trial showed some positive effects; phase 3 trial is underway
 - Seemingly inhibited NFT formation
- **PBT2** - billed as a plaque buster but no cognitive effects were seen
 - In Phase 2 stages



Resveratrol – in Phase 3 trials

- Chemical produced by certain plants when under attack by pathogens. Resveratrol is found in the skin of red grapes and is a constituent of red wine; it has also been produced by chemical synthesis.
- In mouse and rat experiments, anti-cancer, anti-inflammatory, blood-sugar-lowering and other beneficial cardiovascular effects of resveratrol have been reported.
 - Most of these results have yet to be replicated in humans.
- Implications for AD?
 - Animal study reported that dietary supplementation with resveratrol significantly reduced plaque formation.
 - In humans it is theorized that oral doses of resveratrol may reduce beta amyloid plaque associated with aging changes in the brain.



AD 2020?: The Treatment Horizon

- Disease-modifying therapy
- Combination disease-modifying and symptomatic therapy
- Earlier recognition of Alzheimer's disease – retinal scans?
- Integration of biomarkers into clinical practice
 - Spinal fluid
 - Blood
 - Imaging
 - Genetics as well
- Many unanswered questions regarding risk/cause

PREVENTION = HEALTHY AGING



The Memory Wellness Program

The University of Washington & The VA Puget Sound Health Care System

- Free **CONSULTATION** for older adults with memory concerns who are interested in participating in research
- Many different **RESEARCH** opportunities for older adults in our community

Internet: Google "Memory Wellness Program"

South Sound: 253-583-2008

866-638-8813 (toll free)

North Sound: 206-764-2809

888-291-7316 (toll free)

