


Alzheimer's Disease: 2010 Dementia and Decision Making Capacity




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Disclosures

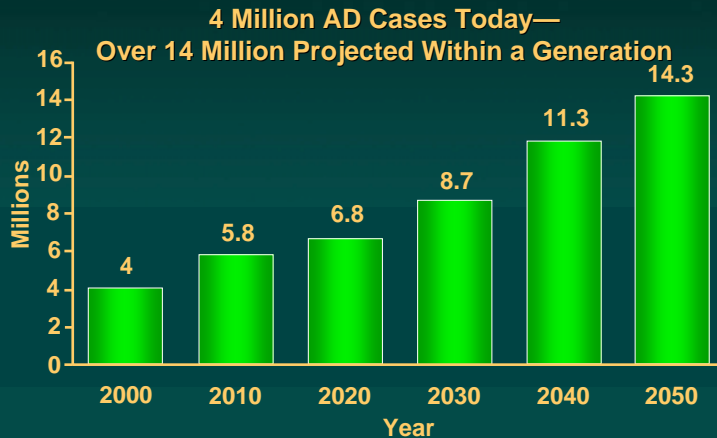
- Funding Support
 - National Institute on Aging (NIA)
 - AAA Foundation for Traffic Safety
 - Missouri Department of Transportation
 - LongerLife Foundation
- Consulting Relationships
 - American Medical Association (AMA)
 - ADEPT
- Speakers Bureau
 - St. Louis Alzheimer's Association
- Medical Director
 - The Rehabilitation Institute of St. Louis
 - Parc Provence
- Drug Industry Sponsored Trials
 - Janssen, Novartis
- Investment/Stock/Equity
 - None





First Quarter: Epidemiology



- Affects > 4 million people in the U.S. (20 million world-wide)
- Results in > 100,000 deaths per year
- Costs > \$100 billion annually

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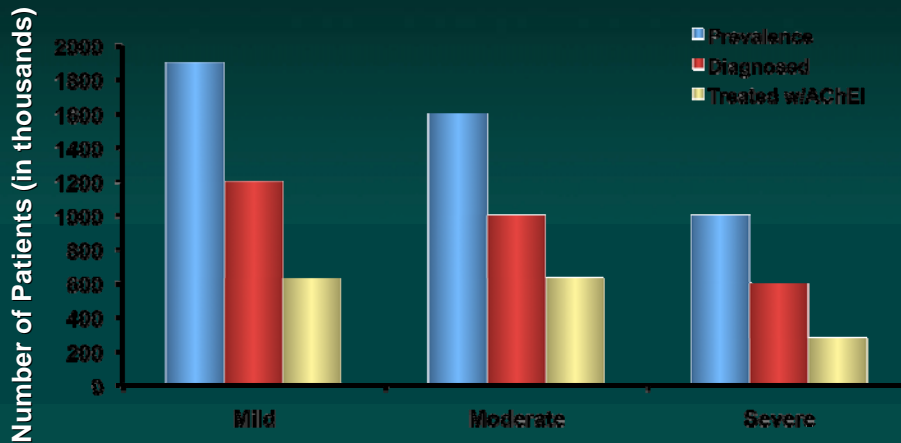
More Facts and Figures

- 5.2 million Americans have AD in 2008
 - Women more commonly affected
 - 16% of women effected over age 71 years
 - 11% of men effected over age 71 years
- 500,000 have dementia under age 65 years
- 13% have AD over age 65 years
- Every 71 seconds, someone develops DAT

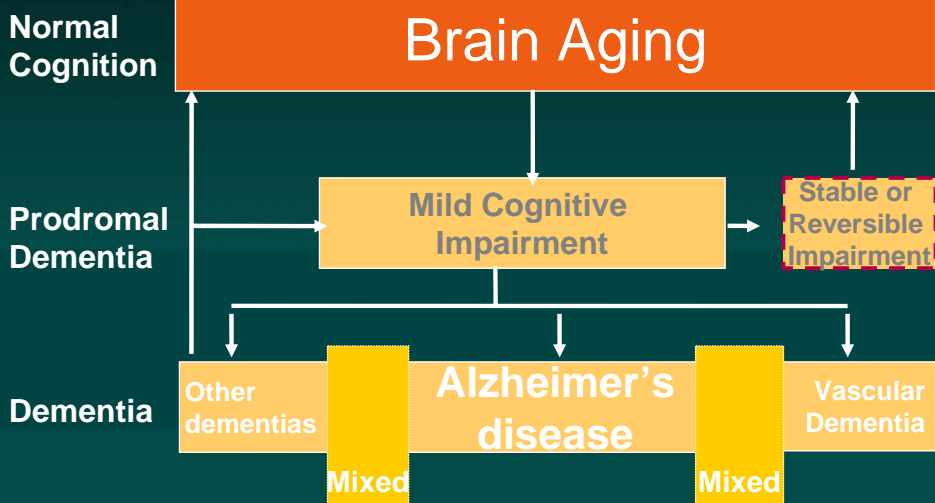
2008 Alzheimer's Disease Facts and Figures

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Prevalence and Treatment Rates



1. Hebert et al. *Arch Neurol.* 2003;60:1119-1122
2. *Datamonitor AD Treatment Algorithms 2002*
3. Market Measures 2003.

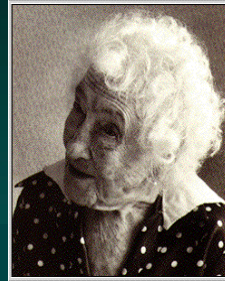


From Golomb, Kluger, Ferris
NeuroScience News, 2000

Risk Factors

■ Maximum Life Span

- Tortoise-150 years
- Human-122 yrs
- Asian elephant-60 yrs
- Lion-25 yrs
- Dog-20 yrs
- Rabbit-15 yrs
- Rat-4 yrs
- Shrew-2 yrs



Conclusion: Genetics a Major Factor

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Conclusion: Environment a Player

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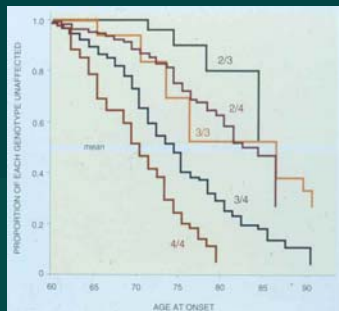
Risk Factors for Sporadic DAT

■ Robust risk factors

- Advanced age
- Family history of DAT
- Down's syndrome
- ApoeE genotype 4

■ Putative risk factors

- Vascular risk factors
 - Systolic hypertension
 - Hypercholesterolemia
 - Diabetes mellitus



■ Putative protective factors

- Exercise
- Nutrition
- Cognitive Stimulation
- Education
- Socialization

Update Risk Factors for Dementia/AD

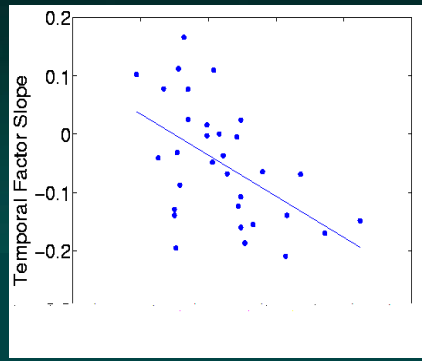
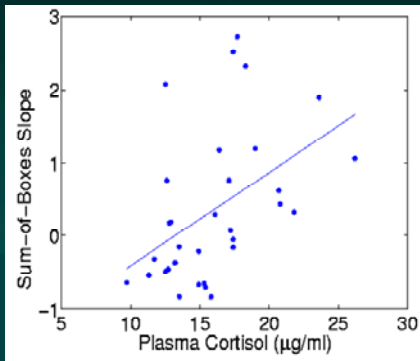
Increased Risk

- Smoking in apoE4- persons (Reitz, Neurology 2007;69:998-1005)
- Inflammatory markers (blood cytokines: IL-6, TNF- α , CRP) (Tan, Neurology 2007;68:1902-1908)
- Insulin resistance; metabolic syndrome (Craft, Alz Dis Assoc Disord 2006;20:298-301; Ranzay, Arch Neurol 2007;64:93-96)

Decreased Risk

- Mediterranean diet: high intake of fish, vegetables, fruits, cereal, unsaturated fatty acids [olive oil], and regular alcohol, and low intake of meat/poultry, dairy products, and saturated fatty acids (Scarmeas, Ann Neurol 2006 59:912-921)
- Alcohol; caffeine (in women) (Solfrizzi, Neurology 2007;68:1790-1799; Ritchie, Neurology 2007;69:563-545)
- Engaged lifestyle (physical, cognitive, social) (Verghese, Neurology 2006;66:821-827); Bennett, Lancet Neurology 2006;5:406-412)

Plasma Cortisol and Progression of Dementia



Combining the two groups of DAT subjects (CDR 0.5 and 1 - n=33), there was a significant positive association between higher 8 AM cortisol levels and worsening dementia rating scores and psychometric tests

From: Csernansky, et al. Am J Psychiatry. 163; 2164-9.

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The Prescription that may add Quality and Quantity to your Life

These Four Legs of the Table can hold you up!!

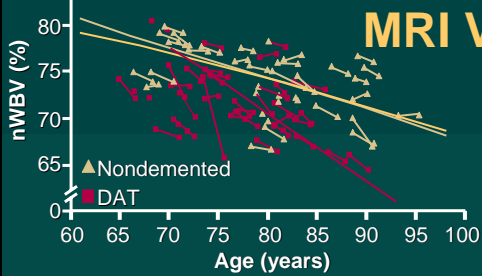
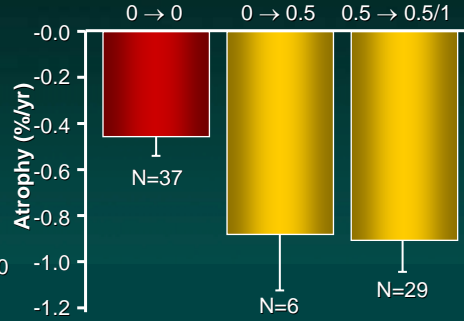
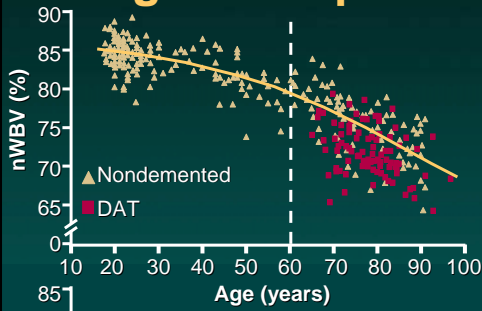
1. Cognitive/Social Stimulation
2. Proper Nutrition
3. Exercise
4. Treat Risk Factors for Vascular Dx



And reduce stress!!!!

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Diagnosis Update



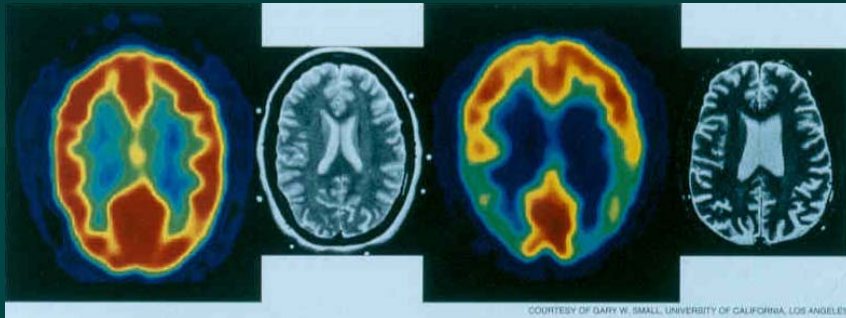
MRI Volumetric Measures

From Fotenos et al. *Neurology*. 2005;64:1032-1039.

nWBV = normalized whole-brain volume, employing head-size correction

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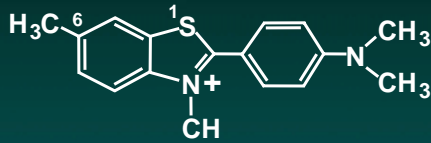
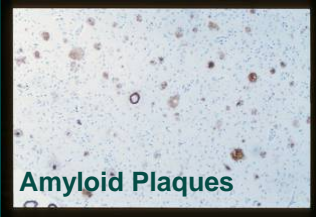
Functional PET Scan Imaging



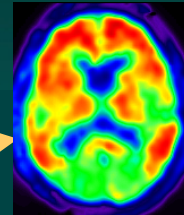
COURTESY OF GARY W. SMALL, UNIVERSITY OF CALIFORNIA, LOS ANGELES

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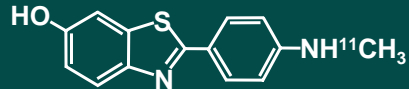
In vivo Amyloid Imaging with Pittsburgh Compound B (PIB) (Klunk et al, Ann Neurol 2004)



Histology - Thioflavin T



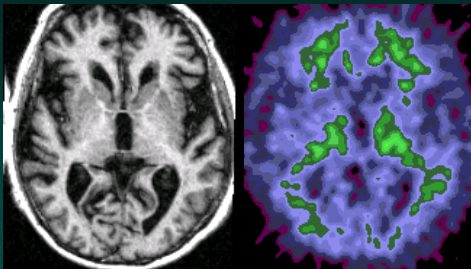
PET Imaging - [11C]6-OH-BTA-1 (PIB)



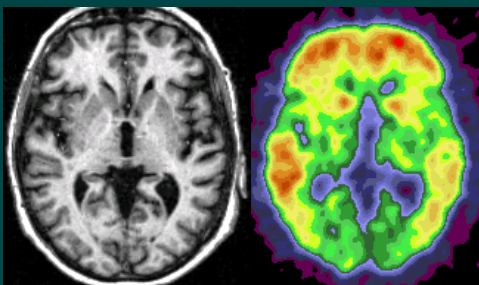
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MRI

PIB PET



No Memory Problems

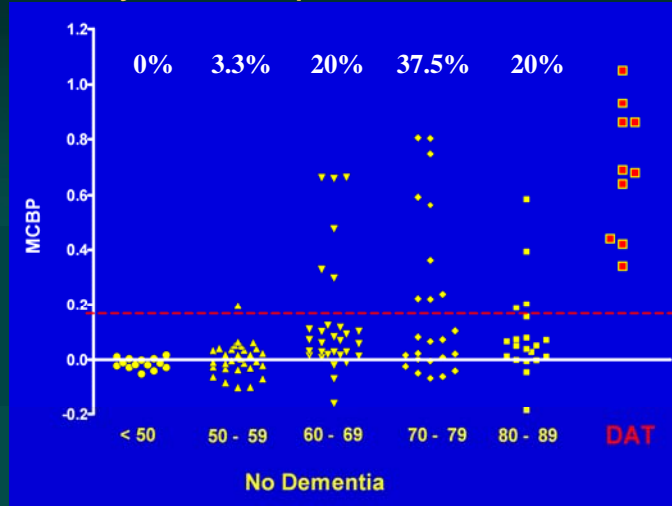


Alzheimer's Disease

Klunk et al., Ann Neurol 2004;55:306-319

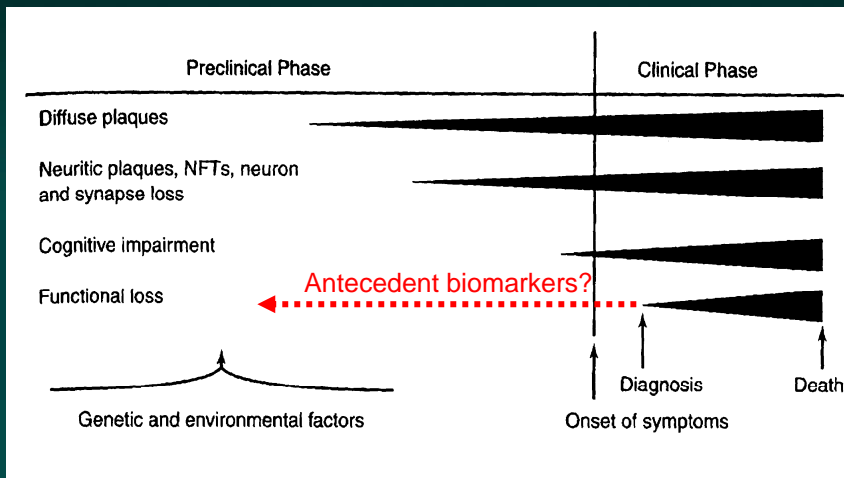
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Mean Cortical PIB Binding By Age Do Amyloid Plaques Predict Dementia?



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Chronic Disease Model of AD

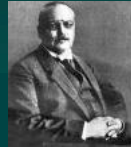


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Dementia: Still a Clinical Diagnosis!

■ DSM-IV dementia

- Memory impairment
- One/more following
 - Aphasia
 - Apraxia
 - Agnosia
 - Dysexecutive function
- Impairments in
 - Occupational function or
 - Social function and
 - Decrease from baseline
- Delirium excluded



APA: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, 2000

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There is a need to r/o Other Causes!

■ Etiologic category

- Endocrine/metabolic*
- Autoimmune/inflammatory
- Infectious
- Neoplastic
- Toxic*
- Sleep disorder**
- Vascular
- Traumatic
- Depression

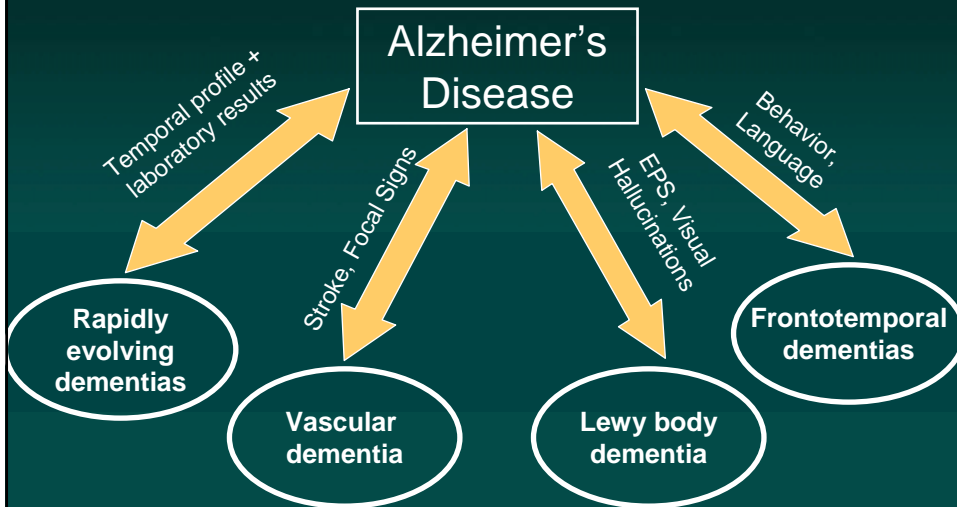


■ Examples

- TSH/B12/renal/liver*
- Vasculitis/SLE/sarcoid/HIV
- Syphilis/lyme/encephalitis
- Meningioma/tumors
- Drugs/heavy metals
- OSA/CSA/PLMD
- Hypertensive encephalopathy
- Mild traumatic brain injury
- Subdural/NPH

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Clues to Differential Diagnosis



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Frontotemporal Dementia (FTD)

■ Red Flags

- Young: 50's-60's age (mean age 56 years)
- Onset of disinhibited or criminal behavior
- Loss of social awareness
- Compulsive behavior
- Distractibility or impulsivity
- Disordered mood (depression or euphoria)
- Stereotyped speech

■ Criteria

- PERSONALITY
 - Early and/or progressive change in personality characterized by difficulty in controlling behavior
- LANGUAGE
 - Early and or progressive changes in language, characterized by problems with expression or severe naming or comprehension

Lund-Manchester, Neary
Working Group on FTD

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LEWY BODY DEMENTIAS
SYMPTOMS AND DIAGNOSTIC CRITERIA

Dementia plus any combination of symptoms on this chart is adequate reason to suspect Lewy body dementia and pursue a differential diagnosis.

Symptom/Area of Deficit	Dementia with Lewy Bodies (DLB)	Parkinson's Disease Dementia (PDD)
Dementia	Required ✓ Usually prominent Usually prominent	Required Core Core Core Core
1. Memory impairment 2. Language impairment 3. Visuo-spatial function impairment 4. Executive function impairment		
Parkinsonism	Core (can occur around the same time OR after dementia)	PD diagnosis required (usually years before dementia)
Fluctuating Cognition	Core Usually prominent ✓	✓ Core Supportive
1. Reduced attention 2. Excessive daytime sleepiness		
Visual hallucinations	Core	Supportive
Severe neuroleptic sensitivity	Suggestive	✓
REM sleep behavior disorder	Suggestive	✓
Changes in personality and mood		Supportive
1. Depression 2. Anxiety	Supportive ✓	✓
Delusions	Supportive	Supportive
Apathy	✓	Supportive
Hallucinations in other modalities	Supportive	✓
Severe autonomic dysfunction	Supportive	✓
Repeated falls and syncope	Supportive	✓
Transient, unexplained loss of consciousness	Supportive	
Diagnostic Criteria:	Probable DLB: <ul style="list-style-type: none"> Dementia plus 2 Core Dementia plus 1 Core, 1 Suggestive Possible DLB: <ul style="list-style-type: none"> Dementia plus 1 Core Dementia plus 1 Suggestive 	Probable PDD: <ul style="list-style-type: none"> Parkinson's, Dementia plus 2 Core Possible PDD: <ul style="list-style-type: none"> Parkinson's, Dementia plus 1 Core

✓ = Common symptom not required for diagnosis.

www.lbd-usa.org - Lewy Body Dementia Association - 1.800.4RW100

Treatment Update

- Nature of the illness
- Extent of Disability
- Social and psychological needs/support services
- Future changes/prognosis
- Treatment
- Referral
- Readings: The 36-Hour Day
- Alzheimer Association
- Legal issues



Driving and Dementia: When is it time to hang up the keys?

■ Green Light

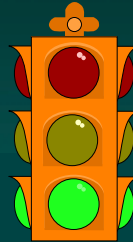
- No red flags
- Monitor at intervals

■ Yellow Light

- Red flags
- Refer for driving evaluation

■ Red light

- Driving Cessation/Retirement

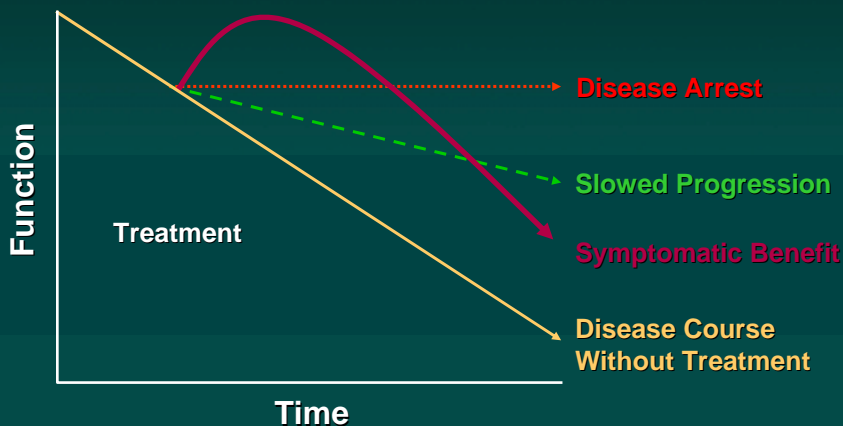


1. Know how to evaluate
2. Know how to refer
3. Know legal/ethical issues

Top 10 Strategies to Help Drivers Retire

- 1) Hiding/filing down the keys
- 2) Do not repair the car
- 3) Remove the car by loaning, giving or selling
- 4) Disable the car
- 5) Replace keys
- 6) Raise concern about losing life savings
- 7) Ask non-family member to talk with driver
- 8) Ask physician to “prescribe” driving retirement
- 9) Use a contract (see At the Crossroads guide)
- 10) Initiate the revocation process

Possible Treatment Outcomes



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Mild Cognitive Impairment (MCI)

- Intermediate state
- Defined as subjective memory complaints
- Objective memory loss (> 1.5 or 2.0 SD's)
- No impairment in function/cognitive domains
- Conversion to dementia is ~2-15% per year
 - Increased rates with advancing ages
- New studies raise questions about treatment



Peterson RC. Neurology 2006;67:S12-13

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Donepezil and Vitamin E in MCI

- Primary endpoint (progression to AD at 3y)
 - No treatment effect for donepezil or Vitamin E
- Additional analyses
 - No treatment effect for Vitamin E at any point
 - Donepezil showed decreased risk for progression to AD:
 - Relative reduction of 58% at 1y and 36% at 2y
 - For 3y in subset with one or more apoE ϵ 4 allele
- No unexpected side effects



From: Petersen RC et al., NEJM 2005;352:2379-2388.

FDA-Approved Pharmacotherapy in Alzheimer's Disease

Cholinesterase Inhibitors

- Tacrine
- Donepezil
- Galantamine
- Rivastigmine
- Approved for use in mild to moderate AD

N-Methyl-D-Aspartate (NMDA)–Receptor Antagonist

- Memantine
- Approved for use in moderate to severe AD

Cholinesterase inhibitors (ChEIs)

■ Issues

- Early vs. Late Stage
- Relative stabilization of cognitive abilities
- Behavioral pathology develops less often
- Neuropsychiatric symptoms may be responsive

• Side Effects

- GI
- Urinary
- Muscle
- Sleep
- Bradycardia
- Oral

Arch Intern Med. 2009 May 11;169(9):867-73. Syncope and its consequences in patients with dementia receiving cholinesterase inhibitors: a population-based cohort study.

Memantine (Namenda)



Mechanism: NMDA receptor antagonist, reduces calcium efflux into cells and is thought to be neuroprotective

Dose: 5m po qd and titrate up weekly until 10 mg bid. However, reduce dosage for renal failure.

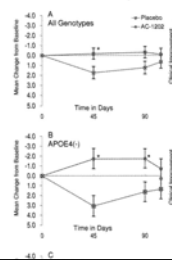
Benefits: similar to Ach-, benefits are probably realized through relative cognitive stability, moderate dementia, dual therapy

Side effects: constipation, headache, dizziness, and confusion

Caprylic Triglyceride: Axona

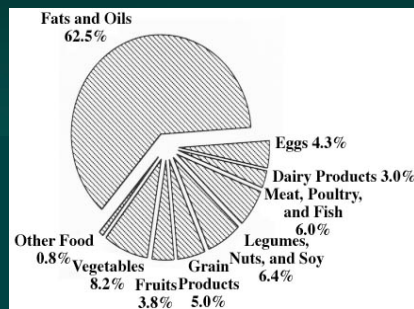
- Theory: AD is characterized by early and region specific declines in cerebral glucose metabolism
- Axona is metabolized in the liver to a ketone body providing neurons with an alternative fuel (BHB)
- A medical food, supplied
- MMSE 14-24
- N=152 with AD
- ApoE4- group showed differences

Hendershot et al., Farr LJ, et al. Nutrition and Metabolism 2009; 6:31, epub



Vitamin E: To E or not to E?

- Type
Alpha Tocopherol
- Brand
Check with pharmacist
- Dose
400 IU for treatment
Hold on larger doses
- Side effects
- Cost
- Drug Interactions



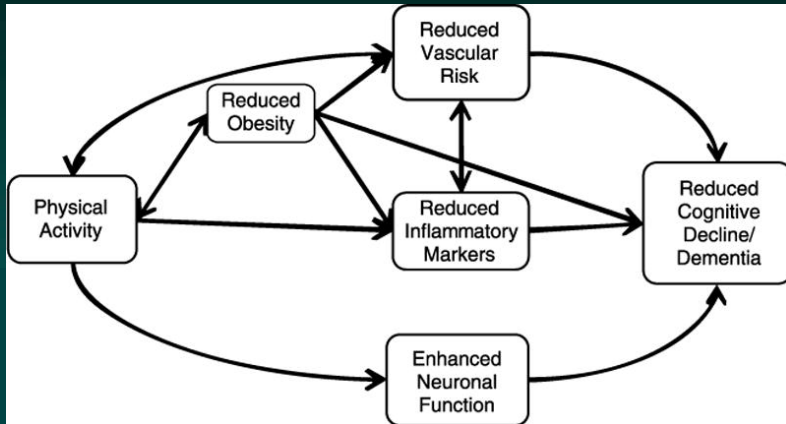
Issues with Antipsychotic Treatment

- Clinical Benefit
- Side Effects
- Black Box Warning
- Mechanism causing Mortality
- Recent Trials Indicating Lack of Efficacy
- Why do we still use them?
- Agents of Choice
- Legal Issues
- Research

Diet and Genes: Nutritional Genomics

- Genetic profiles with customized nutrition plans
 - Green Tea: may silence genes that fuel breast cancer
 - Broccoli: may boost genes that protect against heart disease
 - Soybeans: may affect genes involved in prostate cancer
 - Turmeric (yellow curcumin): suppresses genes that fuel inflammation
 - Garlic: slows metabolism which produces carcinogens
- Foods to consider in prevention or treatment of DAT
 - Fruits/Vegetables/Fish/others?





Barnes, DE, Whitmer RA, and Yaffe K. Physical Activity and Dementia: The need for prevention trials. *Exercise and Sport Sciences Review*. 2007; 35(1) 24-29.

Why is More Funding Needed???

■ Crunch the Numbers

- Multiple Individuals and Professionals Impacted
- Psychological, Functional, Physical, Social, and Financial Burden

"We spend \$100 billion a year on a disease no one in his right mind would want, but fight that with only \$650 million and declining," said Dr. David A. Bennett, director of the Rush Alzheimer's Disease Center at Rush University Medical Center in Chicago. "It just makes no sense."



<http://mednews.wustl.edu/news/page/normal/7360.html>

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Assessment of Patients' Competence to Consent to Treatment Applebaum P. NEJM 2007; 357: 1834-40.

- A 75-year-old woman with type 2 diabetes mellitus and peripheral vascular disease is admitted with a gangrenous ulcer of the plantar aspect of her left foot. A surgical consultation results in a recommendation for a below-the-knee amputation, but the patient declines the procedure on the grounds that she has lived long enough and wants to die with her body intact. Her internist, who has known her for 15 years, is concerned that she has been increasingly confused over the past year and now appears to be depressed. How should her physician determine whether her decision is a competent one?

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Assessment of Patients' Competence to Consent to Treatment Applebaum P. NEJM 2007; 357: 1834-40.

- Competency and capacity in this article are interchangeable
- Legal system cannot handle all situations
- Good reason to continue the traditional method of having physicians determine patients' capacity
- One study noted that 50% of 300 inpatients with acute conditions were estimated to be competent for medical treatment they were receiving. The medical team identified only 25% of this group as being impaired.
- Common conditions: Dementia/Stroke/Psychiatric Illnesses
- Common sites: ICU/Nursing Homes

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**Assessment of Patients' Competence to
Consent to Treatment Applebaum P. NEJM
2007; 357: 1834-40.**

- Studies indicate
 - Physicians are often unaware of capacity of their patients
 - Physician performance of capacity is often suboptimal
 - Physicians may not know what standard to apply
 - There may be an incorrect assignment of incapacity based on diagnostic categories or performance on psychometric tests.

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**Assessment of Patients' Competence to
Consent to Treatment Applebaum P. NEJM
2007; 357: 1834-40.**

- Attempt to strike a balance between respecting the patients autonomy and protecting the patient from the consequences of a bad decision.
- The presumption intrinsic to a modern democracy is that the vast majority of persons are capable of making their own decisions
- Thus, only patients with impairment that puts them at the bottom of the performance curve should be considered incompetent.

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**Assessment of Patients' Competence to
Consent to Treatment Applebaum P. NEJM
2007; 357: 1834-40.**

- Legal Standards for Decision-making Capacity
 - The ability to communicate choice
 - To understand relevant information
 - To appreciate the medical consequences of the situation
 - To reason about treatment choices
- Studies have shown differences between physicians ability to perform competency assessments when provided specific instructions (.16-.46).

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**Assessment of Patients' Competence to
Consent to Treatment Applebaum P. NEJM
2007; 357: 1834-40.**

- Communicating a Choice
 - Have you decided whether to follow your doctor's (or my) recommendation for treatment?
 - Can you tell me what your decision is?
 - What is making it hard for you to decide? (if no decision)

.....

**Assessment of Patients' Competence to
Consent to Treatment Applebaum P. NEJM
2007; 357: 1834-40.**

■ Understanding Relevant Information

- Please tell me in your own words what your doctor (or I) told you about:
 - The problem with your health
 - The recommended treatment
 - The possible benefits and risks (or discomforts) of treatment
 - Any alternative treatments and their risks and benefits
 - The risks and benefits of no treatment

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**Assessment of Patients' Competence to
Consent to Treatment Applebaum P. NEJM
2007; 357: 1834-40.**

■ Appreciate the Situation and its Consequences

- What do you believe is wrong with your health now?
- Do you believe that you need some kind of treatment?
- What is treatment likely to do for you?
- What makes you believe it will have that effect?
- What do you believe will happen if you are not treated?
- Why do you think your doctor has (or I have) recommended this treatment?

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**Assessment of Patients' Competence to
Consent to Treatment Applebaum P. NEJM
2007; 357: 1834-40.**

- Reason about the Options
 - How did you decide to accept or reject the recommended treatment?
 - What makes (chosen option) better than the alternative option?

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**Assessment of Patients' Competence to
Consent to Treatment Applebaum P. NEJM
2007; 357: 1834-40.**

- MacArthur Competence Assessment Tool
 - Most widely used in research
 - Structured interview incorporates information specific for the decision-making capacity decision
 - Takes ~20 minutes and results in a point score
 - High inter-rater reliability
 - Probably best reserved for difficult cases and those that are likely need to be resolved in court



CASE EXAMPLES

- Resolution of the Diabetic Case
- The Case of the Woman who Refused Hip Surgery
- My Dementia Practice
 - Issues of DPA/Guardianship
 - Evaluation of Cognitive Domains
 - IADL's
 - Psychometric Tests
 - Psychotropic Agents