

Reality CME: Alzheimer's Video Vignettes

Cincinnati, OH

October 29, 2008
4:00 PM – 5:15 PM



Session 6: Reality CME: Alzheimer's Video Vignettes

Learning Objectives

- As a result of the video presentation, be able to discuss the challenges and importance of early diagnosis of Alzheimer's disease (AD).
- List 2 optimal treatment approaches for AD based on patient characteristics such as the degree of cognitive impairment (mild, moderate, and severe).

Faculty

Daniel D. Christensen, MD

Clinical Professor of Psychiatry
Clinical Professor of Neurology
Adjunct Professor of Pharmacology
University Of Utah Neuropsychiatric Institute
Salt Lake City, Utah

Dr Christensen is clinical professor of psychiatry, clinical professor of neurology, and adjunct professor of pharmacology at the University of Utah School of Medicine in Salt Lake City, Utah. He was born in Chicago, though he grew up in Utah, and has been at the University of Utah since 1965—as a student from 1965 to 1972, a resident in psychiatry from 1972 to 1976, and since as a member of the faculty.

His research career began as a student in the Department of Chemistry where he completed projects in high-temperature thermodynamics and organic synthesis—receiving research awards from the American Chemical Society and University of Utah Department of Chemistry. Through medical school years he had the privilege of serving on the research team of the renowned hematology team of Maxwell Wintrobe and George Cartwright where his work on iron metabolism received the Student American Medical Association and Bush Memorial Research Awards. Research interests have since included basic science problems, such as the use of STM/AFM microscopy to define the structure of brain receptors, and clinical practice questions, such as the safety and efficacy of various new medications for depression, anxiety, schizophrenia and dementia. Current projects center on psychiatric genetics and Alzheimer's disease and he serves as a consultant to 3 genetic biotechnology firms.

He is the recipient of numerous teaching awards including several times being named “Outstanding Professor” at the University of Utah School of Medicine. His schedule of invited lectures number over 100 per year and have included every state and many foreign countries.

Faculty Financial Disclosure Statement

The presenting faculty reported the following:

Dr Christensen is a consultant for Bayer Healthcare; Bristol-Myers Squibb; Designer Genes, Inc.; Eisai, Inc.; GlaxoSmithKline; Janssen Pharmaceutical Products; Jazz Pharmaceuticals LP; Eli Lilly and Company; Myriad Genetics, Inc.; Novartis Pharmaceuticals Corporation; NPS Pharmaceuticals; Pfizer Inc.; RiboMed; Solvay Pharmaceuticals, Inc.; and Wyeth-Ayerst Laboratories. He is on the advisory boards for Eisai, Inc; GlaxoSmithKline; Jazz Pharmaceuticals; Myriad Pharmaceuticals; and Pfizer Inc. Dr Christensen is on the speakers bureau for Abbott Laboratories; Bayer Healthcare; Bristol-Myers Squibb Company; Eisai, Inc.; GlaxoSmithKline; Janssen Pharmaceutical Products; Eli Lilly and Company; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Solvay Pharmaceuticals; Upjohn, Inc.; and Wyeth-Ayerst Laboratories. He also conducts research for Abbott Laboratories; Bristol-Myers Squibb; Designer Genes, Inc.; Eccles Institute of Human Genetics; GlaxoSmithKline; Janssen Pharmaceuticals; Myriad Genetics; Novartis Pharmaceuticals Corporation; NPS Pharmaceuticals; Organon USA; Pfizer Inc.; RiboMed; Solvay Pharmaceuticals; and Wyeth-Ayerst Laboratories.

Drug List

There are no drugs mentioned in this presentation.

Suggested Reading List

Hebert LE, Scherr PA, Scherr JL, et al. Alzheimer disease in the US population: prevalence estimates using the 2000 census. *Arch Neurol*. 2003;60:1119-1122.

Kaduszkiewicz H, Zimmermann T, Beck-Bornholdt HP, van den Bussche H. Cholinesterase inhibitors for patients with Alzheimer's disease: systematic review of randomised clinical trials. *BMJ*. 2005;331:321-327.

Rosenberg RN. Translational research on the way to effective therapy for Alzheimer disease. *Arch Gen Psychiatry*. 2005;62:1186-1192.

Reisberg B, Doody R, Stöffler A, et al. Memantine in moderate-to-severe Alzheimer's disease. *N Engl J Med*. 2003;348:1333-1341.

Sloane PD, Zimmerman S, Suchindran C, et al. The public health impact of Alzheimer's disease, 2000-2050: potential implication of treatment advances. *Annu Rev Public Health*. 2002;23:213-231.

Gandy S. The role of cerebral amyloid β accumulation in common forms of Alzheimer disease. *J Clin Invest*. 2005;115:1121-1129.

Alzheimer's Disease Diagnosis to Death

Daniel D. Christensen, M.D.
Clinical Professor of Psychiatry
Clinical Professor of Neurology
Adjunct Professor of Pharmacology
University of Utah

AD in Primary Care

- Approximately 80% of patients consulted a primary care physician (PCP) first for AD symptoms¹
- Nearly 60% of patients with AD go undiagnosed in the primary care setting¹
- Barriers to diagnosis and treatment of AD in primary care
 - AD symptoms are not easily recognized
 - Diagnosis of AD is too difficult
 - Reimbursement for diagnosis of AD is difficult

¹Knopman et al. *J Am Geriatr Soc.* 2000;48:300-304.

Video - Baseline

Common Assessment Tools

- There are many assessment tools available
- Some are easier to administer than others
 - MMSE¹
 - Clock drawing test (CDT)²
 - MiniCog³
- Primary care physician or staff members can administer in ≤15 minutes

¹Folstein et al. *J Psychiatr Res.* 1975;12:189-198.
²Wolf-Klein et al. *J Am Geriatr Soc.* 1989;37:730-734.
³Borson et al. *J Am Geriatr Soc.* 2003;1451-1454.

Mini-Mental State Examination (MMSE)
 Make the patient comfortable and establish rapport. Ask questions in the order listed. Total possible score is 30.

Maximum Score	Score	Item
5	5	ORIENTATION: What is the date (month, day, year)?
5	5	ORIENTATION: What are we doing here (hospital, clinic, etc.)?
3	3	REGISTRATION: Name 3 common objects.
5	5	ATTENTION: Serial 7's test.
3	3	RECALL: Ask for the 3 common objects named during registration.
2	2	LANGUAGE: Name a "pen" and "pencil".
1	1	LANGUAGE: Repeat the following: "The old man, or boy."
3	3	LANGUAGE: Follow a 3-stage command: "Take a paper in your right hand, fold it in half, and put it on the floor."
1	1	LANGUAGE: Read and obey the following: CLOSE YOUR EYES.
1	1	LANGUAGE: Write a sentence.
1	1	LANGUAGE: Copy the following design.

Handwritten note: It seems the world is in good trouble.


Handwritten score: 70/100 Baseline

Baseline

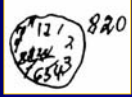


Clock at 2:30

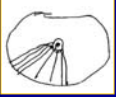
Clock Drawing Test




A
MMSE = 30



B
MMSE = 20



C
MMSE = 14




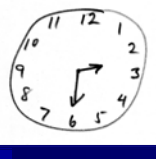




D
MMSE = 19

Patients with dementia

Adapted from Nolan et al. In: Richter et al, eds. *Alzheimer's Disease: A Guide to Practical Management, Pt. II*. St. Louis, Mo: Mosby Yearbook; 1994:81-95.

Clocks at 2:30

MiniCog:

A simple tool for cognitive assessment

3-Word Registration
+
Clock Draw
+
3-Word Recall

Note: If problem identified using MiniCog, MMSE should be performed.

Borson et al. *Int J Geriatr Psychiatry*. 2000;15:1021-1027.
Borson et al. *J Am Geriatr Soc*. 2003;51:1451-1454.

MiniCog Assessment

MINICOG

↓

Recall = 0
Likely IMPAIRED

Recall 1 - 2

Recall = 3
Probably NOT IMPAIRED

↓

Clock Abnormal
Likely IMPAIRED

Clock Normal
Possibly IMPAIRED

Borson et al. *Int J Geriatr Psychiatry*. 2000;15:1021-1027.
Borson et al. *J Am Geriatr Soc*. 2003;51:1451-1454.

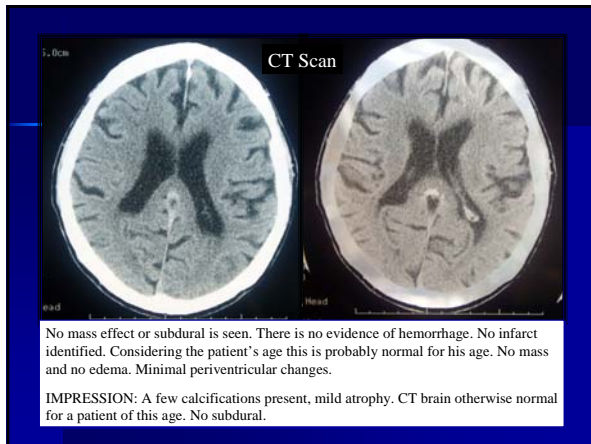
Baseline - Marinus

Weight = 151 lbs
BP = 130 / 70

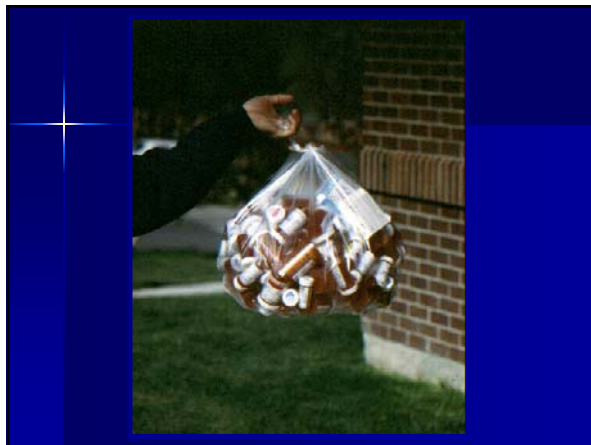
Only complaint - occasional joint pain (? RA)
Physical exam - no abnormalities
Alcohol / tobacco use - None
Medications - Vitamins and Fenoprofen, 600mg qid prn

Baseline - Marinus

COMPREHENSIVE METABOLIC		Range	Units
Panel:			
Sodium	142	137-145	mmol/L
Potassium	4.3	3.5-5.0	mmol/L
Chloride	105	98-109	mmol/L
CO2	27	23-28	mmol/L
Glucose	104	85-110	mg/dL
BUN	20	8-21	mg/dL
Creatinine	1.2	0.6-1.3	mg/dL
Calcium	9.3	8.8-10.2	mg/dL
Protein, Total	7.1	6.0-8.0	g/dL
Albumin, Total	3.4	2.9-4.8	g/dL
Bilirubin, Total	0.8	0.2-1.2	mg/dL
Alkaline Phosphatase	78	44-101	U/L
AST (SGOT)	24	7-19	U/L
CBC WITH DIFFERENTIAL			
WBC	6.5	3.8-10.8	10 ³ /mm ³
RBC	4.61	4.48-5.80	10 ⁶ /mm ³
Hemoglobin	15.0	13.7-16.7	g/dL
Hematocrit	45.4	40-54.0	%
MCV	88.3	(79.8 - 97.3)	fL
MCH	22.6	(26.3 - 32.5)	pg
MCHC	31.1	32.0-36.0	g/dL
RDW	12.1	12.1-15.3	%
Platelets	223	150-450	10 ³ /mm ³
MPV	9.5	8.6-10.1	fL
Differential type			
Neutrophil %	47.5	38.7-79.8	%
Lymphocyte %	39.9	27.4-48.8	%
Monocyte %	11.2	0.2-10.7	%
Eosinophil %	1.2	0.0-5.7	%
Basophil %	0.2	0.0-0.9	%
Neutrophils, Abs Count	2.1	0.8-6.8	10 ³ /mm ³
Lymphs, Abs Count	1.8	1.2-3.4	10 ³ /mm ³
Monocytes, Abs Count	0.5	0.2-0.9	10 ³ /mm ³
Eosinophils, Abs Count	0.1	0.0-0.5	10 ³ /mm ³
Basophils, Abs Count	0.0	0.0-0.2	10 ³ /mm ³
TNII	2.33	0.45-4.67	U/ml



- ### Potentially reversible causes of Dementia
- D Drugs
 - E Endocrinopathies
 - M Metabolic disorders
 - E Emotional depression
 - N Nutritional deficiencies
 - T Tumor / trauma
 - I Infirmities of the senses
 - A Arteriosclerosis



- ### Potentially reversible causes of Dementia
- D Drugs
 - E Endocrinopathies
 - M Metabolic disorders
 - E Emotional depression
 - N Nutritional deficiencies
 - T Tumor / trauma
 - I Infirmities of the senses
 - A Arteriosclerosis

- ### Instrumental ADL's
- Using transportation (personal &/or public)
 - Managing money
 - Cooking
 - Shopping
 - Using the telephone
 - Managing medications
 - Housekeeping / Laundry

- ### Interactive Question
- What is the diagnosis ?
1. Alzheimer's Disease
 2. Vascular Dementia
 3. Mild Cognitive Impairment
 4. Normal Aging

Features that favor the Dx of Alzheimer's Disease

- Age 65 or older
- Insidious onset
- Gradual progression
- Prominent memory difficulty
- No focal signs / sx
- No gait abnormalities

Early Symptoms of AD: ABC

- Early functional symptoms (activities) may include:
 - Difficulty driving
 - Difficulty selecting clothes
 - Problems at work
- Early behavioral symptoms may include:
 - Subtle changes in personality
 - Social withdrawal
 - *Depression Irritability*
- Early cognitive symptoms may include:
 - Trouble keeping appointments
 - Difficulty finding words
 - Misplacing objects

Alzheimer's Disease DSM IV Diagnostic Criteria

Memory impairment

One or more:

aphasia, agnosia, apraxia, impaired executive function

ADL's

Impaired functioning

Insidious onset, Gradual progression

Other potential causes

Ruled out

Features that favor the Dx of Vascular Dementia

- Abrupt onset
- Focal neurological signs & symptoms
- Stepwise deterioration
- Atherosclerosis / TIAs
- History of strokes
- History of hypertension

Mild Cognitive Impairment

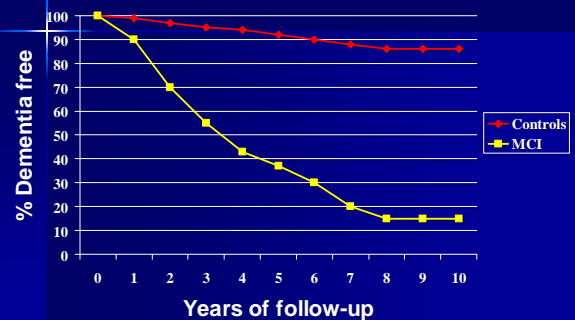
Memory trouble
Subjective complaint
Corroborated
Objective (>1.5 S.D.)

Gen cognitive function
Intact

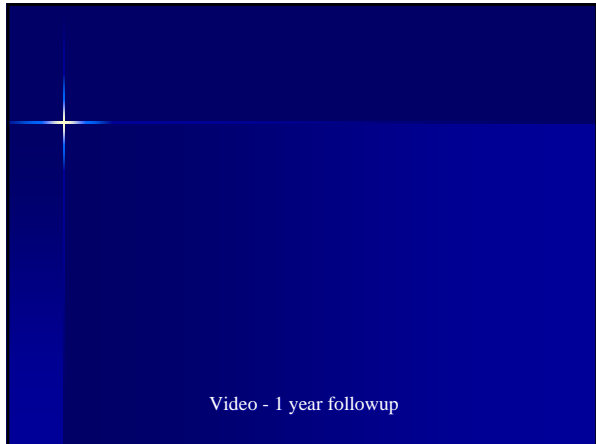
ADLs
No impairment

Peterson et al. Neurology, 2001;56, 1133- 1142

MCI Conversion to Dementia



Petersen, Alzheimer's & Dementia, 2005



MCI Treatment Strategies

- No proven or FDA-approved therapies
- New ICD 9 Code 331.83

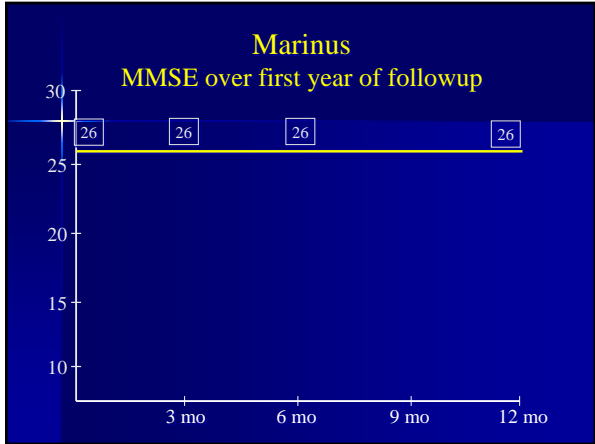
Doraiswamy PM. *Am J Geriatr Psychiatry*. 2003;11:120-122.

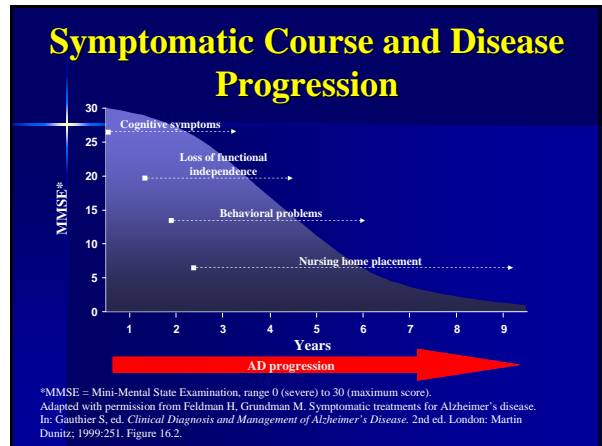
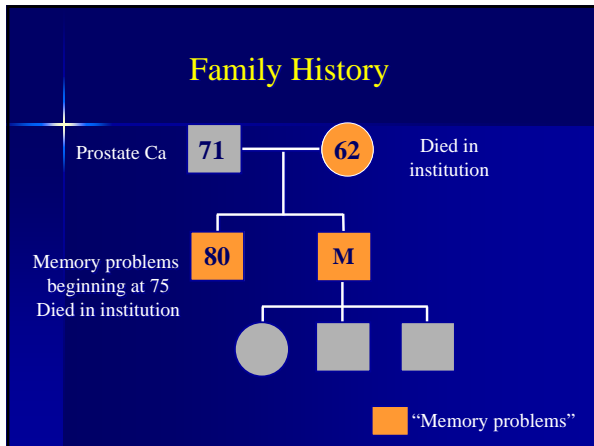
Marinus Pharmacologic Treatment Plan

Vitamin E, 1000 IU / day
Fenoprofen, lower threshold for prn use
Donepezil 5mg / day for 1st month
10 mg / thereafter

One year followup

Clock at 11:10



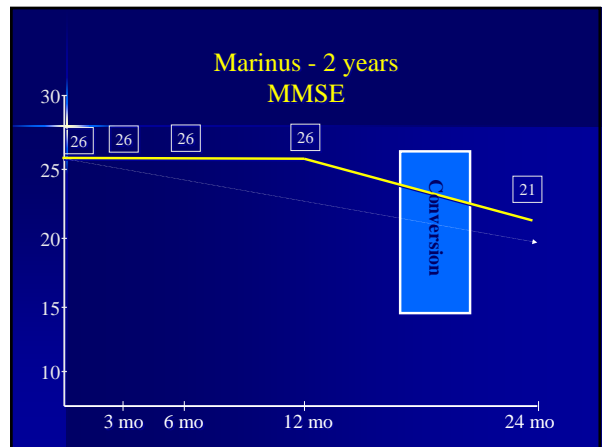
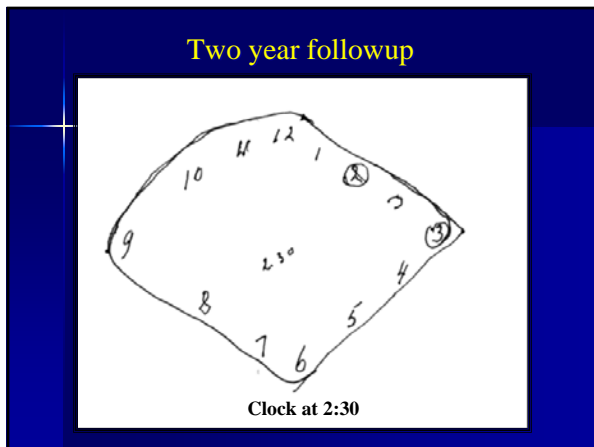


Mini-Mental State Examination (MMSE)

Maximum Score: 30

Section	Score
ORIENTATION	5
REGISTRATION	3
ATTENTION AND SERIAL 7's	4
RECALL	3
LANGUAGE	2
Copy	1
Total	21

Handwritten notes: "It is rather nice weather today"



Nonpharmacologic Treatments

- Sensory stimulation
 - Music therapy¹
 - Light therapy¹
- Social contact
 - One-to-one contact²
 - Pet therapy¹
- Environment
 - Provide a safe environment¹
 - Reduce excess stimulation¹
- Rehabilitation
 - Develop a predictable daily routine³
 - Simplify tasks²
 - Allow independence²
- Recreation
 - Exercise⁴
 - Sorting⁵
 - Games⁶
- Alternative therapies
 - Ginkgo biloba⁷
 - Coenzyme Q10⁸
 - Vitamin E⁹

¹Cohen-Mansfield. *Am J Geriatr Psychiatry*. 2001;9:361-381.
²Cohen-Mansfield and Werner. *J Gerontol A Biol Sci Med Sci*. 1997;52M369-M377.
³Rogers et al. *J Am Geriatr Soc*. 1999;47:1049-1057.
⁴Namazi et al. *J Aging Phys Act*. 1994;2:80-92.
⁵Holmberg. *Arch Psychiatr Nurs*. 1997;11:21-28.
⁶Aronstein et al. *Am J Alzheimer Dis*. 1996;May/June:26-31.
⁷Okun et al. *Arch Neurol*. 1998;55:1409-1415.
⁸Ono et al. *Biochem Biophys Res Commun*. 2005;330:111-116.
⁹Pham and Plakogiannis. *Ann Pharmacother*. 2005;39:2065-2072.

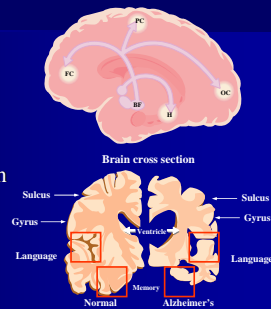
Approved Pharmacologic Treatments for Alzheimer's Disease

- Cholinesterase inhibitors (ChEIs)
 - Donepezil (mild, moderate, severe)
 - Rivastigmine (mild, moderate)
 - Galantamine (mild, moderate)
- N-methyl-D-aspartate (NMDA) receptor antagonist
 - Memantine (moderate, severe)

Physicians' Desk Reference, 60th ed. Montvale, NJ: Thomson Healthcare; 2006.

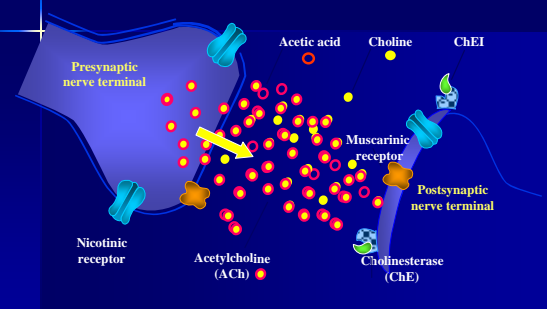
Cholinergic Basis of AD

- Progressive loss of cholinergic neurons in the basal forebrain
- Progressive cortical cholinergic denervation
- Depletion of ACh
- Declines in cognition, function, and behavior



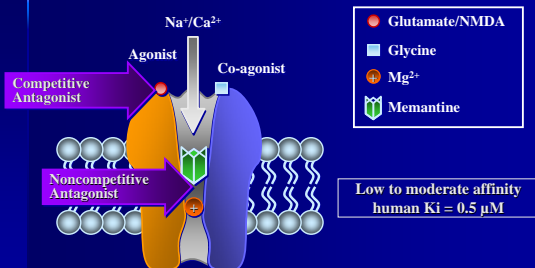
BF = basal forebrain; FC = frontal cortex; PC = parietal cortex; OC = occipital cortex; H = hippocampus.
 Coyle et al. *Science*. 1983;219:1184-1190.

Cholinesterase Inhibition



Nordberg, Svensson. *Drug Safety*. 1998;19:465-480.

Memantine: Noncompetitive NMDA Receptor Antagonist



Physicians' Desk Reference, 60th ed. Montvale, NJ: Thomson Healthcare; 2006.

AD Therapies: Dosing

	Starting Dose	Clinically Effective Dose
Donepezil	5 mg qd	5-10 mg qd
Rivastigmine	1.5 mg bid	3-6 mg bid
Galantamine	4 mg bid	8-12 mg bid
Galantamine ER	8 mg qd	16-24 mg qd
Memantine	5 mg qd	10 mg bid

Physicians' Desk Reference, 60th ed. Montvale, NJ: Thomson Healthcare; 2006.

AD Therapies: Most Common Adverse Events

- Donepezil
 - Nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, and anorexia
- Rivastigmine
 - Nausea, vomiting, anorexia, dyspepsia, and asthenia
- Galantamine
 - Nausea, vomiting, anorexia, dizziness, weight loss
- Memantine
 - Dizziness, headache, constipation, confusion

Physicians' Desk Reference, 60th ed. Montvale, NJ: Thomson Healthcare; 2006.

Video - 3 year followup

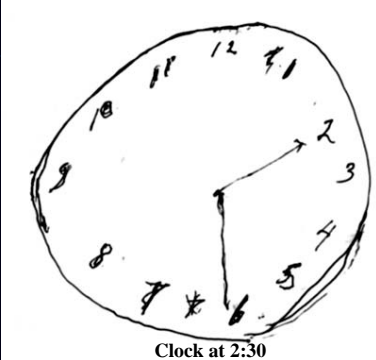
Mini-Mental State Examination (MMSE)²

Make the patient comfortable and establish rapport. Ask questions in the order listed. Total possible score is 30.

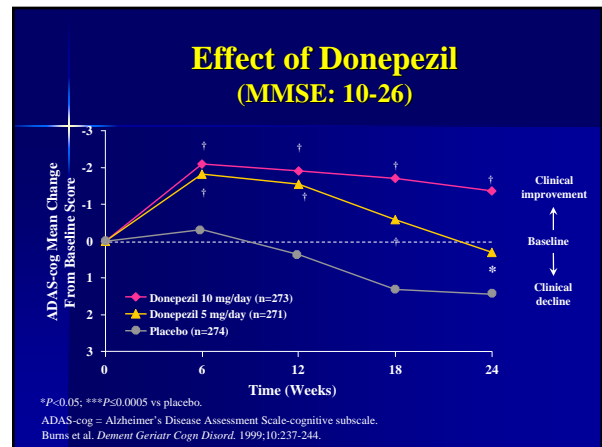
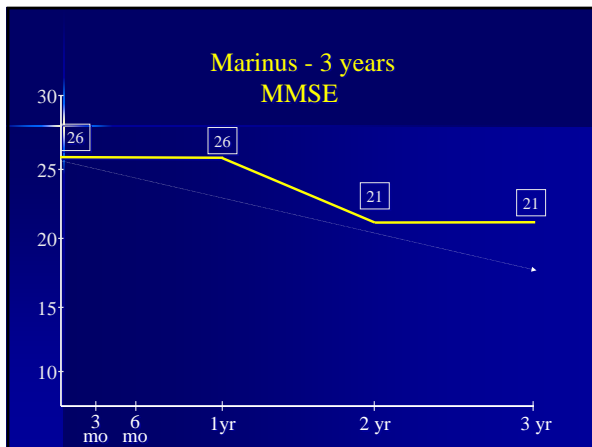
Maximum Score	Scores	ORIENTATION
5	(1)	What is the year? (month)
5	(4)	Where are we? (city) (state)
3	(3)	REGISTRATION
		Name 3 common objects.
		Take 1 second to say each.
		Close 1 point for each one.
		Count trials and record.
5	(4)	ATTENTION AND CALCULATION
		Serial 7's backwards: (See Alternative), spell "WORLD".
		In correct order (10, 9, 8, 7, 6, 5, 4, 3, 2, 1).
3	(3)	RECALL
		Ask for the 3 common objects named during registration above.
		Give 1 point for each correct answer. (Dense recall: answer by name of 2 objects were not remembered during registration.)
2	(2)	LANGUAGE
		Name a "penicillin" and "brand." (2 points)
1	(1)	Repeat the following: "No ifs, ands, or buts."
		Follow a 3-stage command.
		"Take a paper in your right hand, fold it in half, and put it on the floor." (3 points)
1	(1)	Read and obey the following: CLOSE YOUR EYES.
1	(1)	Write a sentence.
1	(1)	Copy the following design.

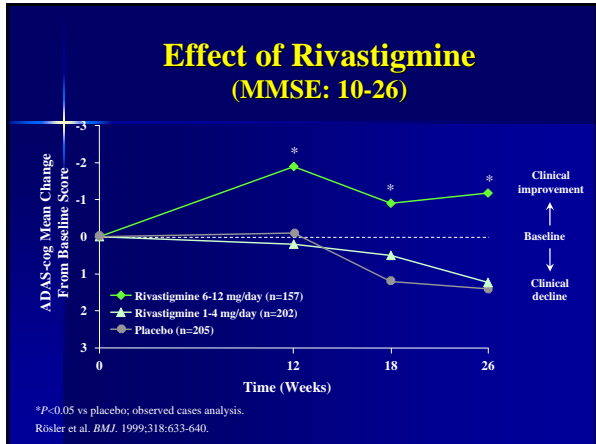
MMSE = 21

Handwritten notes: 7/6/05, 31, "All Lake City, not of the park that what the all the Church of Jesus Christ of Latter Day Saints have sent out of the Saints of the far away part with the one of being."

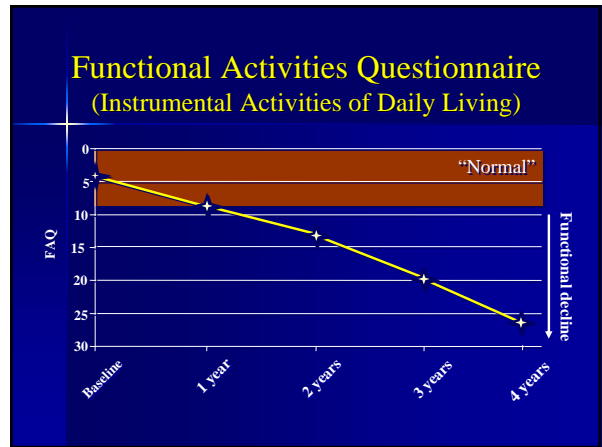
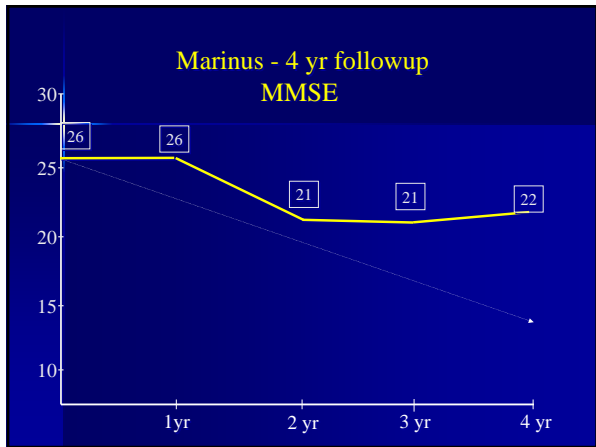


Three year followup





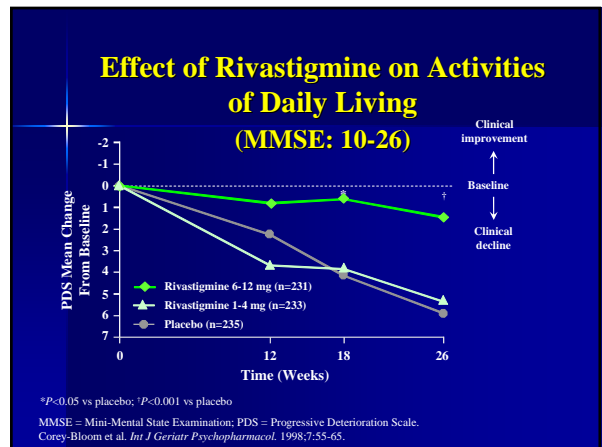
Video - 4 year followup

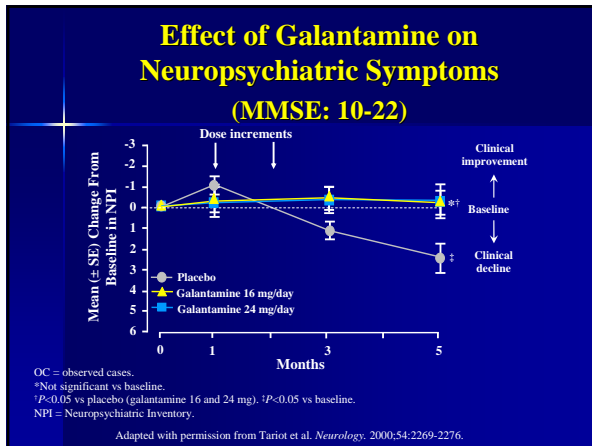


Interactive Question

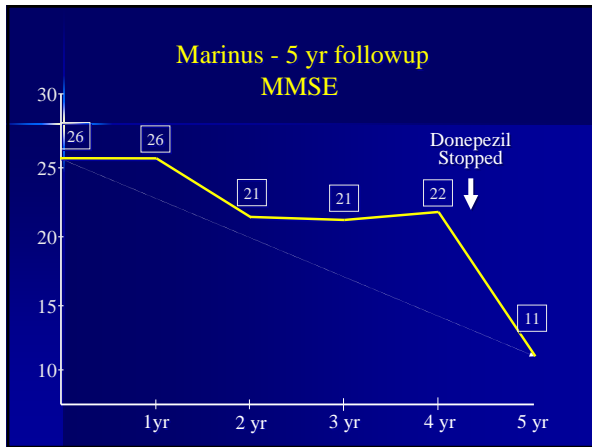
Cholinesterase inhibitors in AD have been shown to benefit:

1. Cognitive symptoms
2. Functional symptoms
3. Behavioral symptoms
4. All of the above





Video - 5 year followup



Interactive Question

When do you terminate ACHEI treatment?

1. At nursing home admission
2. When pt no longer recognizes spouse
3. When behavior becomes unmanageable
4. None of the above

Video - 6 year followup

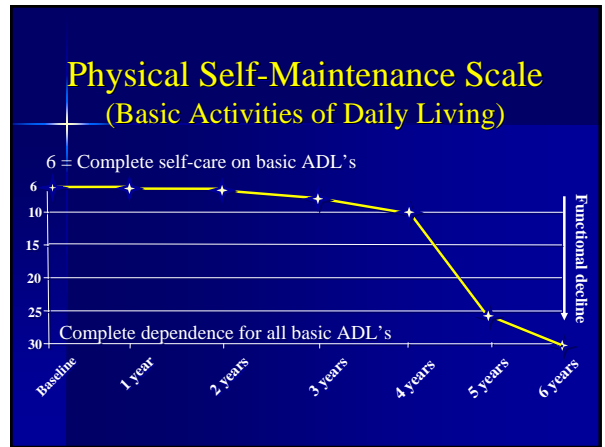
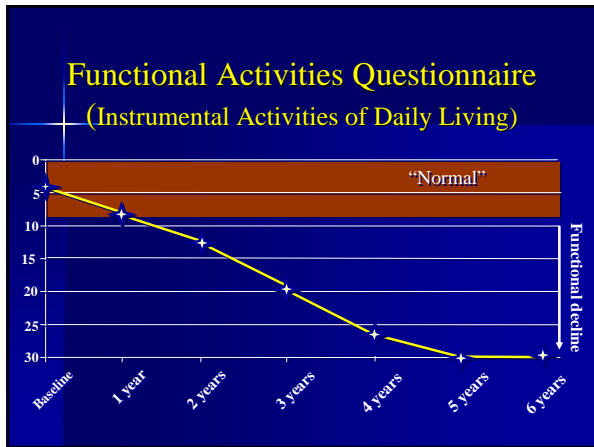
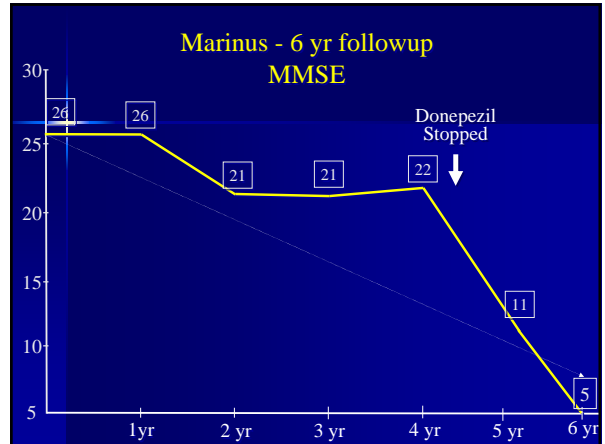
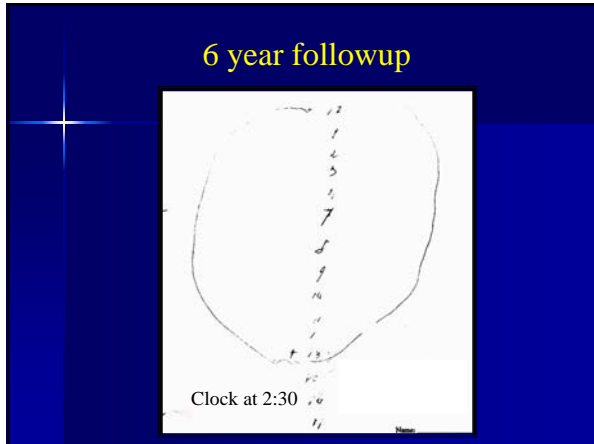
Marinus
6/6/06

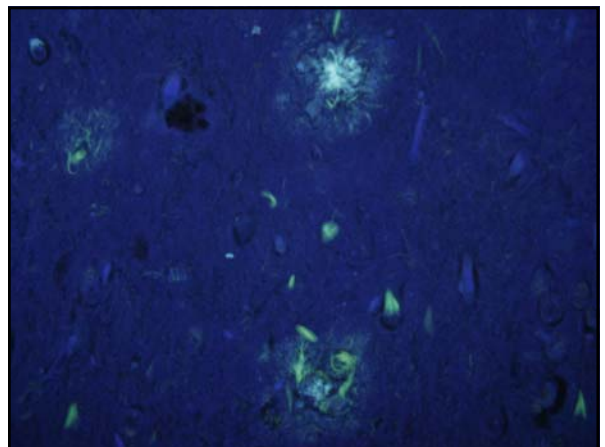
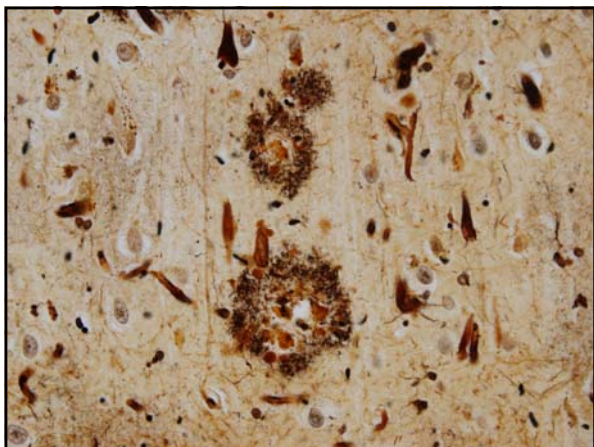
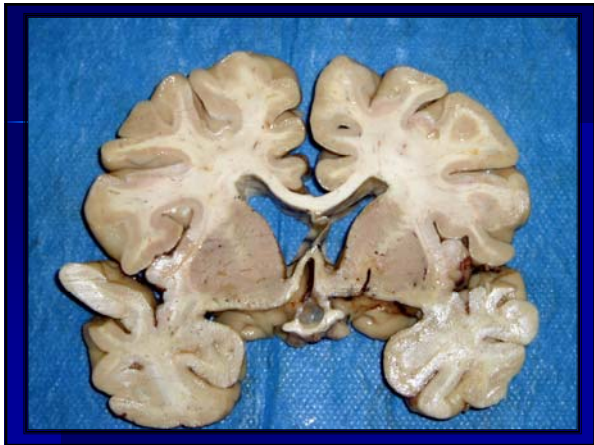
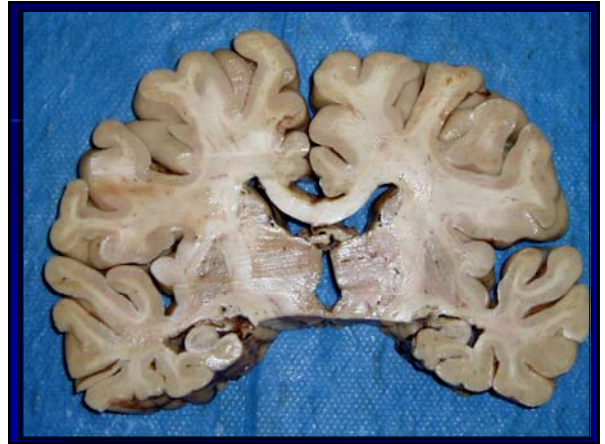
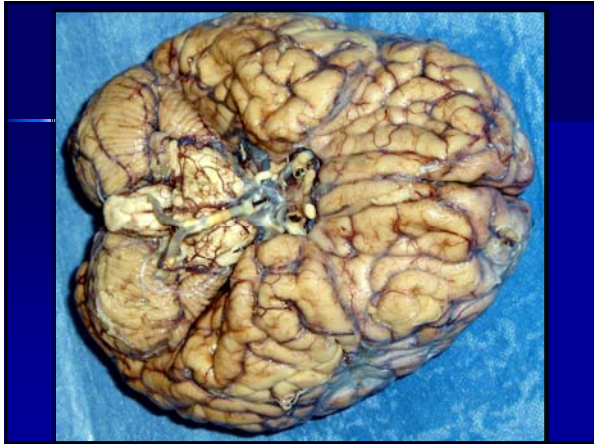
Mini-Mental State Examination (MMSE)^{2,3}

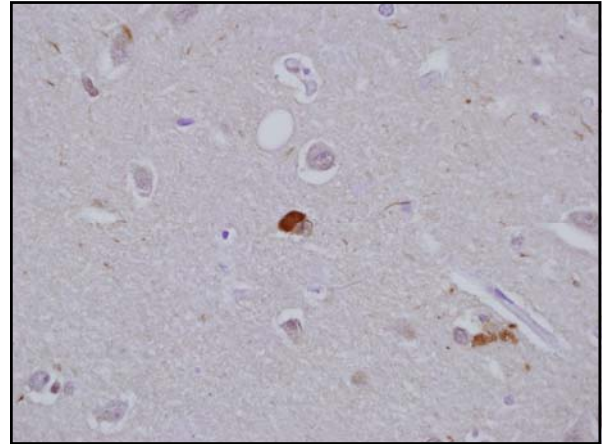
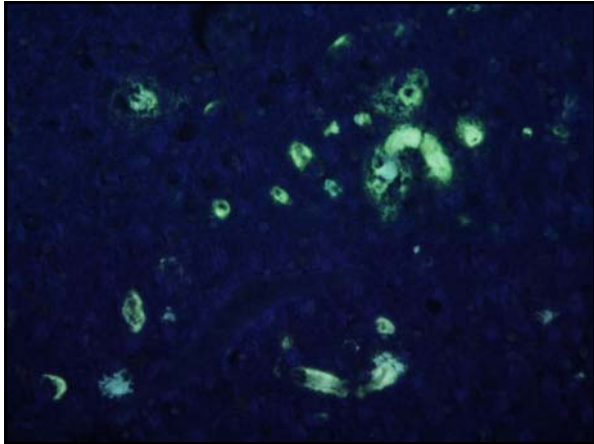
The possible score is 30.
exp. F/M (5)

Maximum Score	Score	
5	(0)	ORIENTATION
5	(0)	What is the capital of Texas? (Austin)
3	(3)	Where are we? (exp. F/M) (exp. or est.) (hospital) (floor)?
		REGISTRATION
		Name 3 common objects (eg, "apple," "table," "banana").
		Take 1 second to say each. Then ask the patient.
		Give 1 point for each correct answer. Then repeat.
		Clearer words and record: Train _____
5	3	ATTENTION AND CALCULATION
		Serial 7's backwards. Stop after 3 answers.
		Alternatively, spell "WORLD" backwards. The
		is correct order (D) _____ O _____ W _____
		RECALL
3	3	Ask for the 3 common objects named during registration above.
		Give 1 point for each correct answer. (Note: recall cannot be tested if all 3 objects were not remembered during registration.)
		LANGUAGE
2	(1)	Name a "country" and "state." (2 points)
1	(1)	Repeat the following: "No ifs, ands, or buts."
3	(1)	Follow a 3-stage command.
		"Take a paper in your right hand,
		hold it in both and put it on the floor" (3 points)
		Read and obey the following: "CLOSE YOUR EYES" (1 point)
1	(1)	Write a sentence. (1 point)
1	(1)	Copy the following design. (1 point)

MMSE = 5

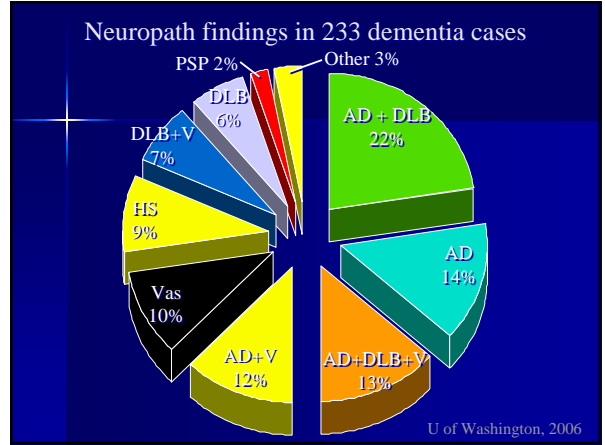






Features that favor the Dx of Lewy Body Dementia

- Visual hallucinations
- Extrapyramidal symptoms (shuffling gait, masked facies, rigidity, gait instability)
- Waxing / waning alertness
- Neuroleptic supersensitivity



Autopsy Diagnosis

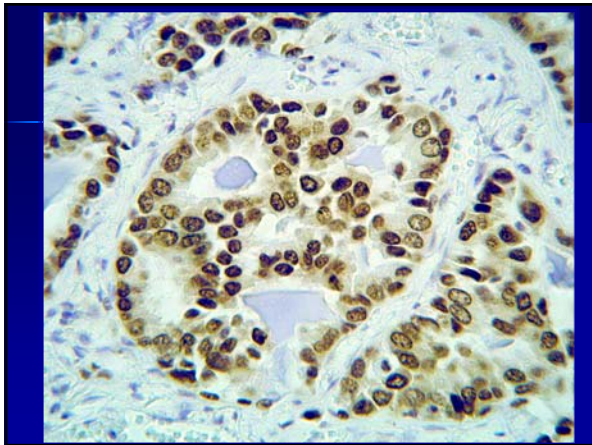
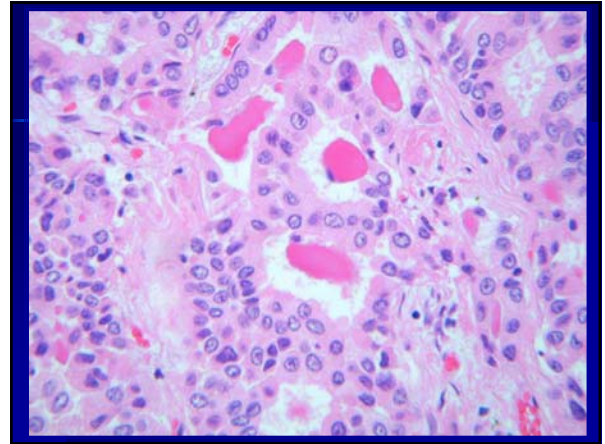
Neuropathology

- Alzheimer's Disease (Braak Stage V, moderate to severe)
- Lewy Body Disease, moderate
- Cerebral Amyloid Angiopathy, mild to moderate
- Cerebral Atherosclerosis, moderate

Autopsy Diagnosis

Cause of Death

Adenocarcinoma of the Lung, metastatic to liver and thyroid



Autopsy Diagnosis

Cause of Death

Adenocarcinoma of the Lung, metastatic to liver and thyroid

Ancillary findings

Atherosclerotic Cardiovascular Disease
Chronic Pyelonephritis
Benign Prostatic Hypertrophy
Diverticulosis

Alzheimer's Disease
Diagnosis to Death

Daniel D. Christensen, M.D.
Clinical Professor of Psychiatry
Clinical Professor of Neurology
Adjunct Professor of Pharmacology
University of Utah