

Reality CME: Alzheimer's Video Vignettes

Houston, TX

November 21, 2008
1:00 PM – 2:15 PM



Session 4: 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.

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

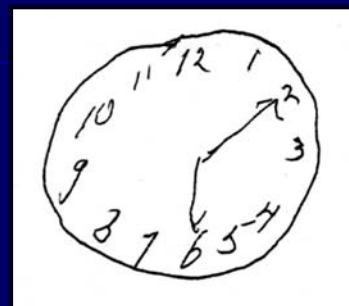
¹Folstein et al. *J Psychiatr Res.* 1975;12:189-198.
²Wolf-Klein et al. *J Am Geriatr Soc.* 1989;37:730-734.
³Borson et al. *J Am Geriatr Soc.* 2003;1451-1454.

Video - Baseline

Mini-Mental State Examination (MMSE)¹
Make the patient comfortable and establish rapport. *Time* _____
Total possible score is 30.


Maximum Score	Score	Instructions
5	(5)	ORIENTATION What is the (day) (month) (year) (state) (city)?
5	(5)	What are we (doing) (eating) (drinking) (wearing) (doing)?
3	(3)	REGISTRATION Name 3 common objects. Take 1 second. Close 1 paper. Count trials as follows.
5	(5)	ATTENTION Serial 7's task. Alternatively, spell "WORLD" backwards. (For score is the number of letters 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. Give 1 point for each correct answer. (None recall cases if objects were not remembered during registration.)
2	(2)	LANGUAGE Name a "penis" and "testis".
1	(1)	Repeat the following: "This is a stick, or beam."
3	(3)	Follow a 3-stage command: "Take a paper in your right hand, fold it in half, and put it on the floor."
1	(1)	Read and obey the following: CLOSE YOUR EYES
1	(1)	Write a sentence.
1	(1)	Copy the following design:

Baseline

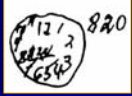


Clock at 2:30

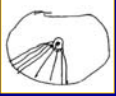
Clock Drawing Test




A
MMSE = 30



B
MMSE = 20



C
MMSE = 14

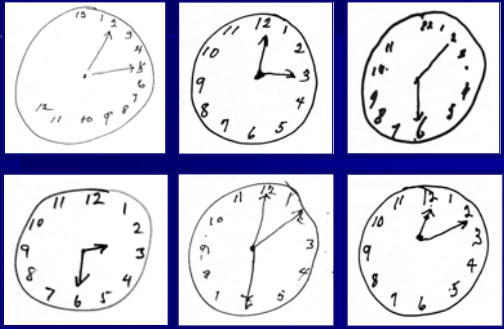


D
MMSE = 19

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:

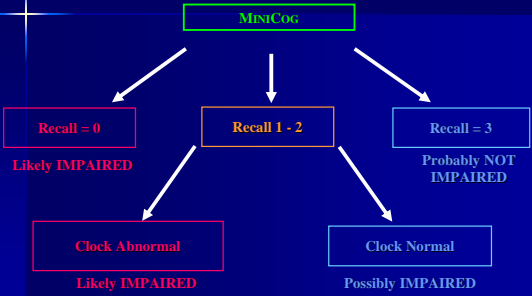
A simple tool for cognitive assessment

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



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

Baseline

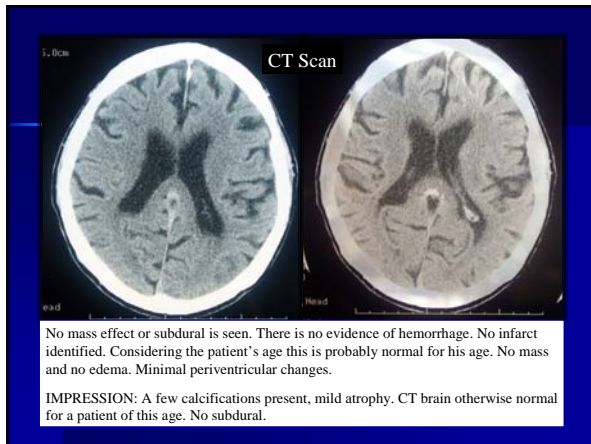
Weight = 151 lbs
BP = 130 / 70

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

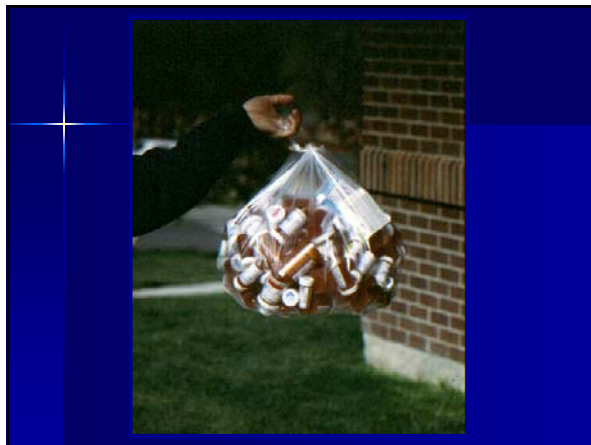
Baseline

COMPREHENSIVE METABOLIC PANEL:		Range	Units
Sodium	142	137-145	mmol/L
Potassium	4.3	3.5-5.0	mmol/L
Chloride	105	98-109	mmol/L
CO2	27	23-29	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:		Range	Units
WBC	6.5	3.8-10.8	10 ⁹ /L
RBC	4.61	4.48-5.80	10 ¹² /L
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 ⁹ /L
MPV	9.9	8.6-10.1	fL
Differential type			
Neutrophil %	47.5	38.7-79.8	%
Lymphocyte %	39.9	27.4-48.8	%
Monocyte %	11.2	4.0-10.7	%
Eosinophil %	1.2	0.5-5.7	%
Basophil %	0.2	0.0-0.9	%
Neutrophils, Abs Count	2.1	0.8-6.8	10 ⁹ /L
Lymphs, Abs Count	1.8	1.2-3.4	10 ⁹ /L
Monocytes, Abs Count	0.5	0.2-0.9	10 ⁹ /L
Eosinophils, Abs Count	0.1	0.0-0.5	10 ⁹ /L
Basophils, Abs Count	0.0	0.0-0.2	10 ⁹ /L
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



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- D Drugs
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- ### 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

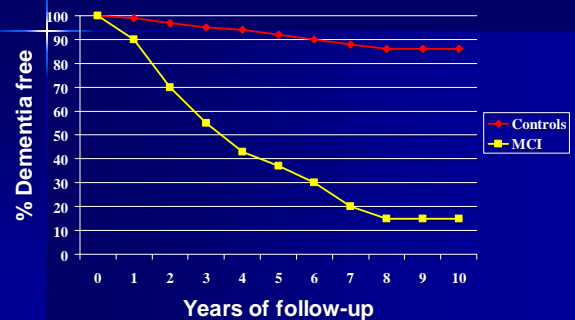
Memory trouble
Subjective complaint
Corroborated
Objective (>1.5 S.D.)

Gen cognitive function
Intact

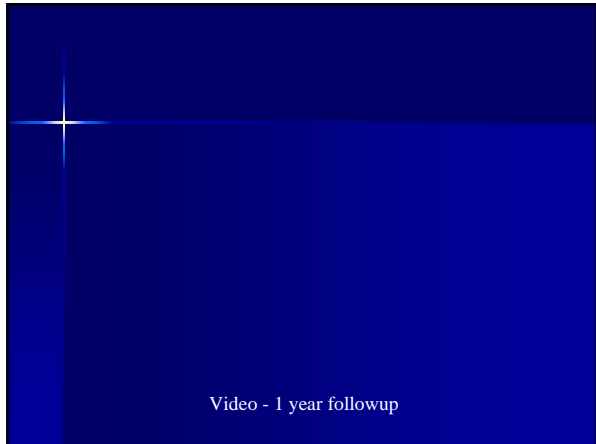
ADLs
No impairment

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

MCI Conversion to Dementia



Petersen, Alzheimer's & Dementia, 2005



Video - 1 year followup

MCI Treatment Strategies

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

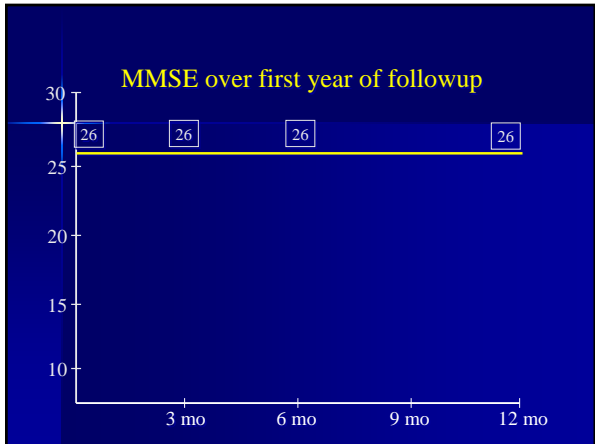
Doraiswamy PM. *Am J Geriatr Psychiatry*. 2003;11:120-122.

Pharmacologic Treatment Plan

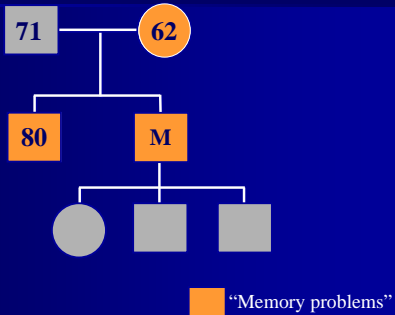
Vitamin E, 1000 IU / day
 Fenpropfen, lower threshold for prn use
 Donepezil 5mg / day for 1st month
 10 mg / thereafter

One year followup

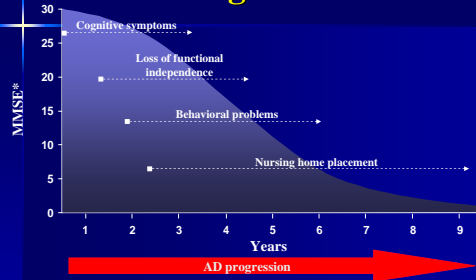
Clock at 11:10



Family History



Symptomatic Course and Disease Progression

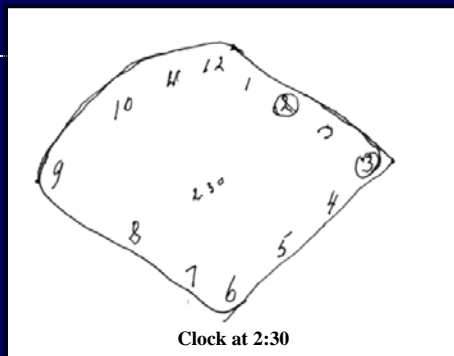


*MMSE = Mini-Mental State Examination, range 0 (severe) to 30 (maximum score). Adapted with permission from Feldman H, Grundman M. Symptomatic treatments for Alzheimer's disease. In: Gauthier S, ed. *Clinical Diagnosis and Management of Alzheimer's Disease*. 2nd ed. London: Martin Dunitz; 1999:251. Figure 16.2.

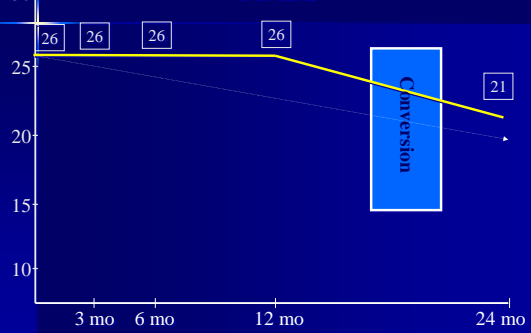
Video - 2 year followup

A Mini-Mental State Examination (MMSE) form with handwritten answers and a drawing. The form includes sections for Orientation, Registration, Attention and Serial 7's backwards, Recall, and Language. The total score is MMSE = 21. A drawing of a house is shown next to the Language section.

Two year followup



2 years MMSE



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.

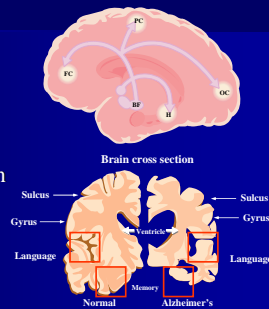
Approved Pharmacologic Treatments for Alzheimer's Disease

- 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.

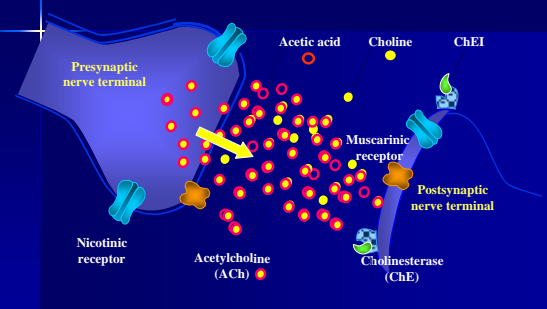
Cholinergic Basis of AD

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



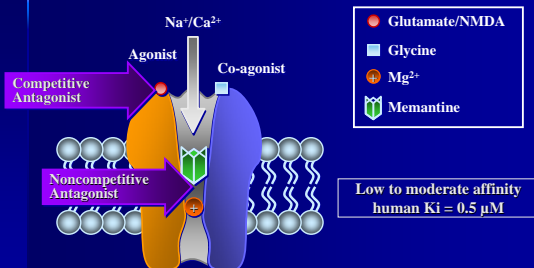
BF = basal forebrain; FC = frontal cortex; PC = parietal cortex; OC = occipital cortex; H = hippocampus.
 Coyle et al. *Science*. 1983;219:1184-1190.

Cholinesterase Inhibition



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

Memantine: Noncompetitive NMDA Receptor Antagonist

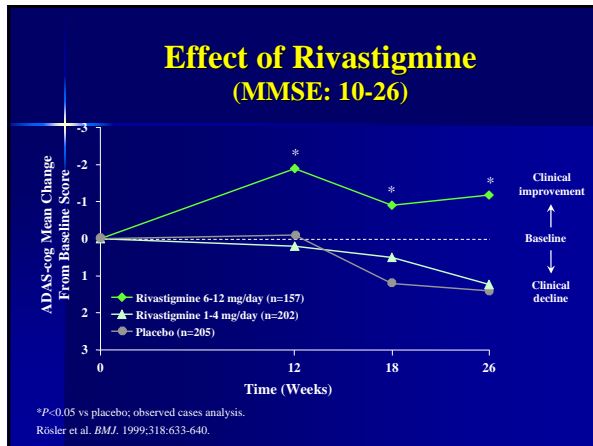


Physicians' Desk Reference, 60th ed. Montvale, NJ: Thomson Healthcare; 2006.

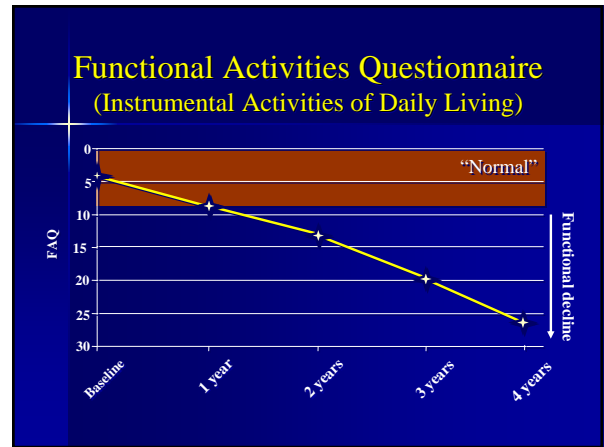
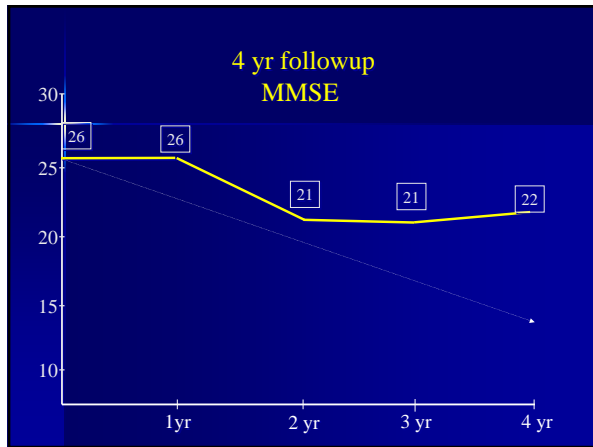
AD Therapies: Dosing

	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.



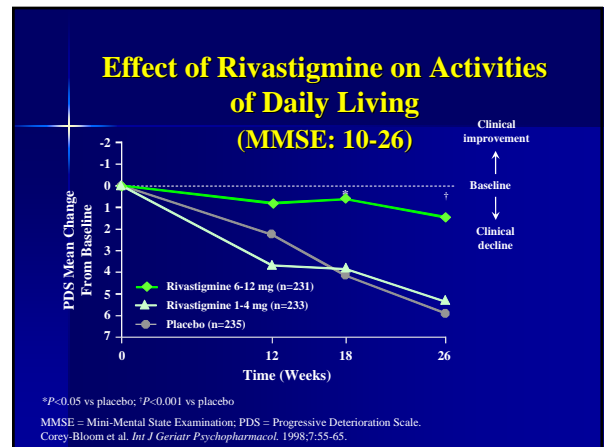
Video - 4 year followup

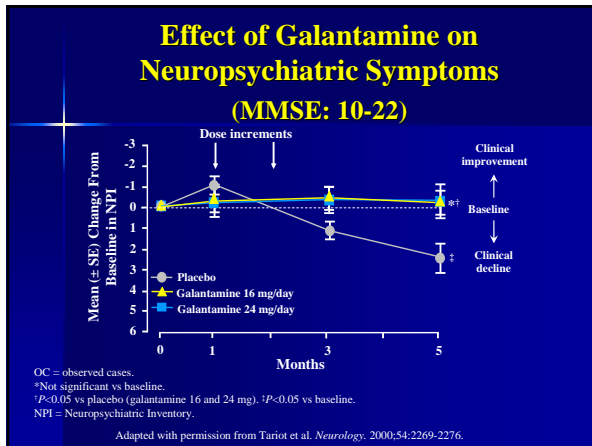


Interactive Question

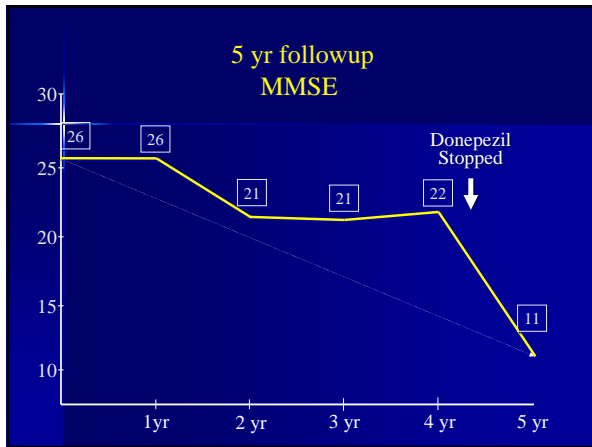
Cholinesterase inhibitors in AD have been shown to benefit:

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

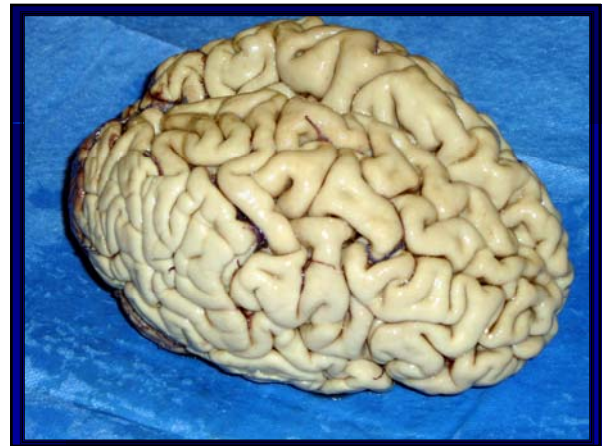
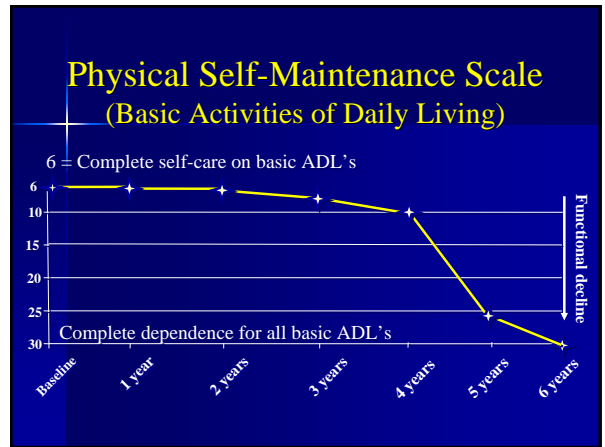
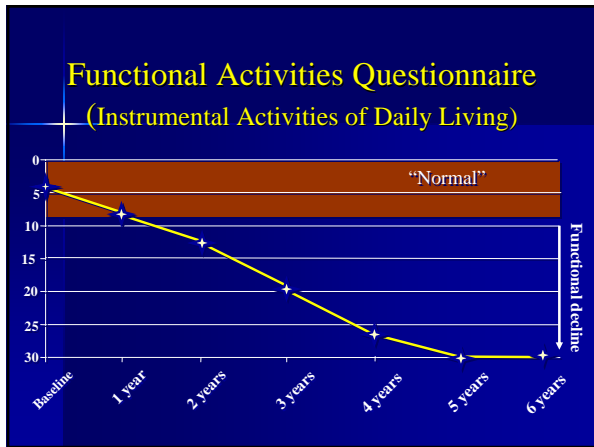
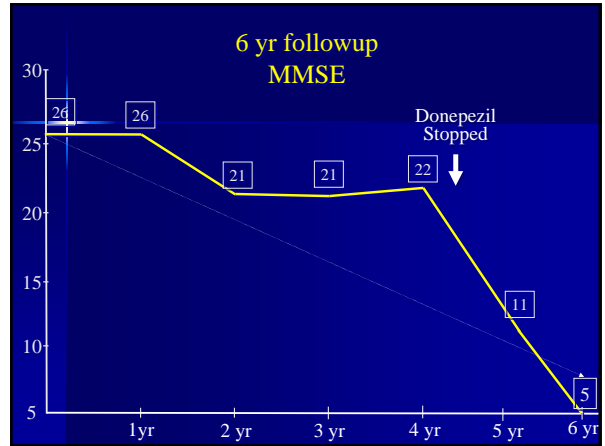
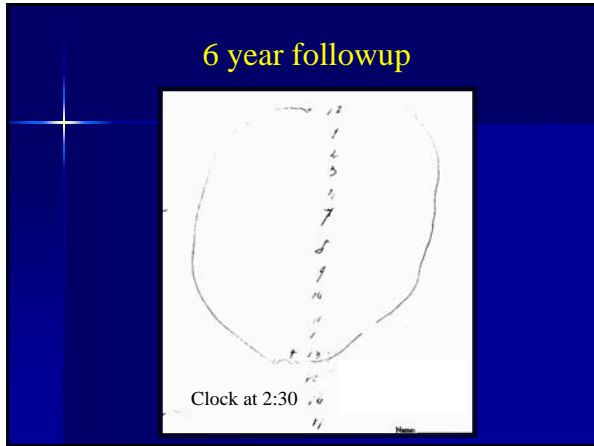
6/6/06

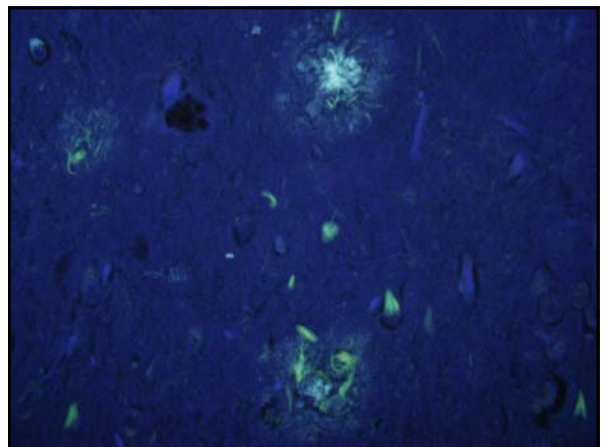
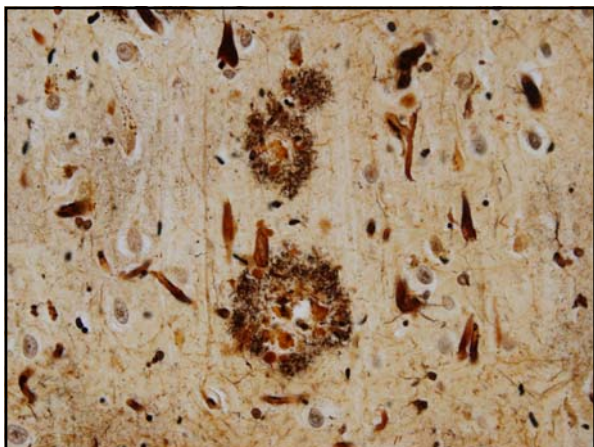
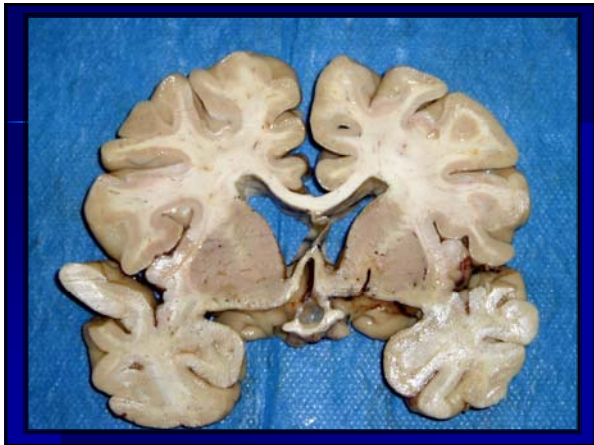
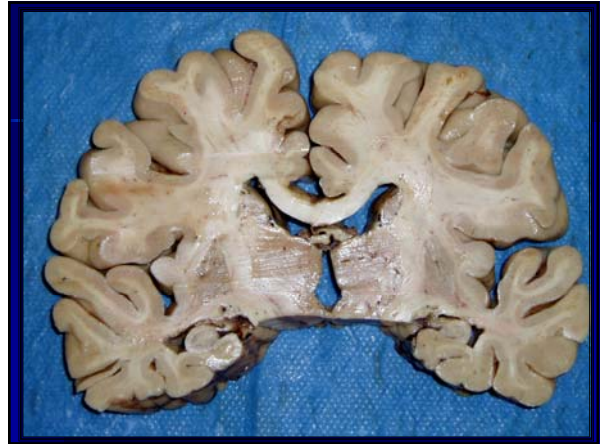
Mini-Mental State Examination (MMSE)^{2,3}

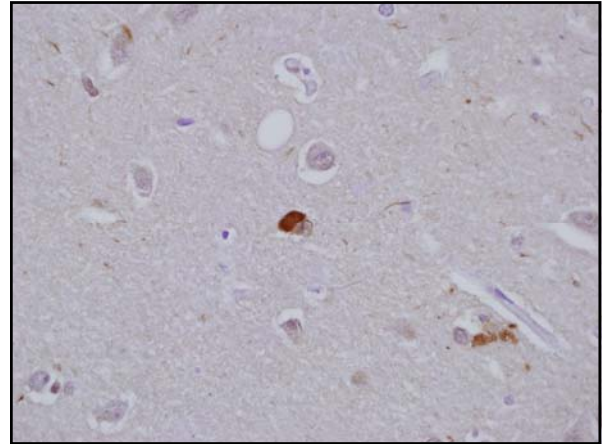
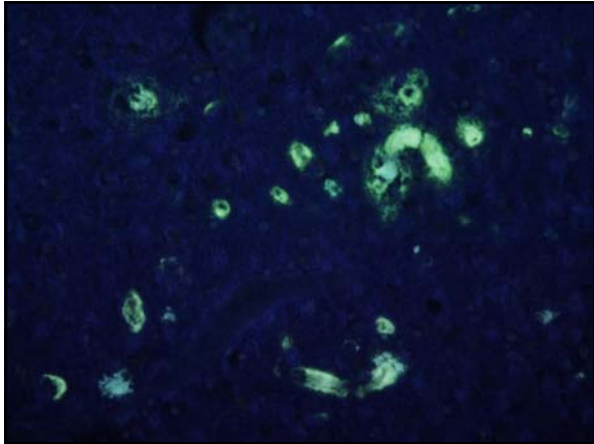
Make the patient comfortable and establish rapport. Ask questions in the order listed. Total possible score is 30.

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

MMSE = 5

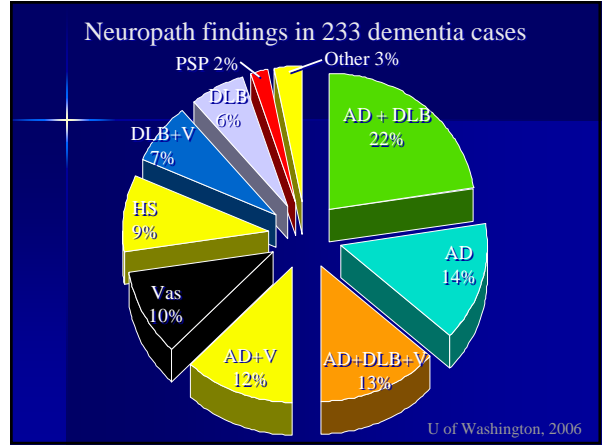






Features that favor the Dx of Lewy Body Dementia

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



Autopsy Diagnosis

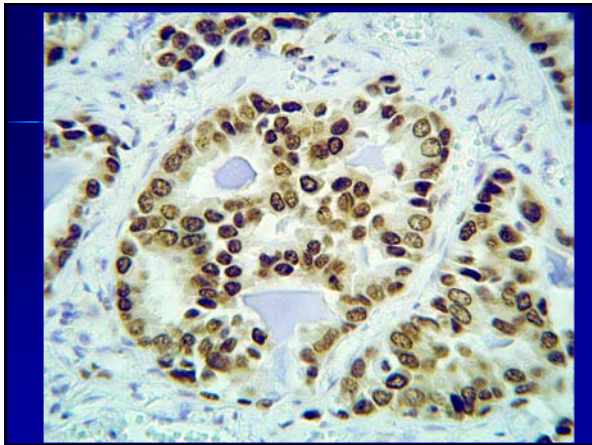
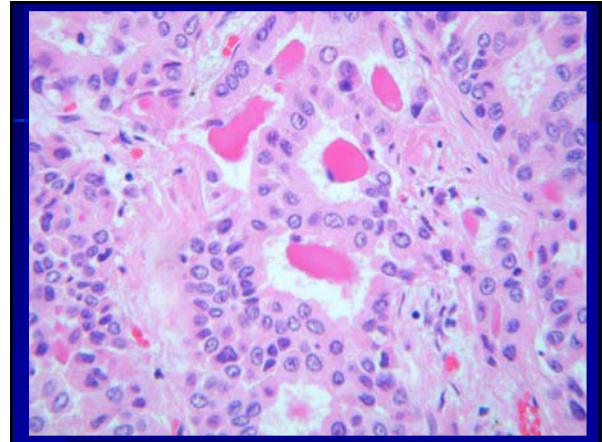
Neuropathology

- 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

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