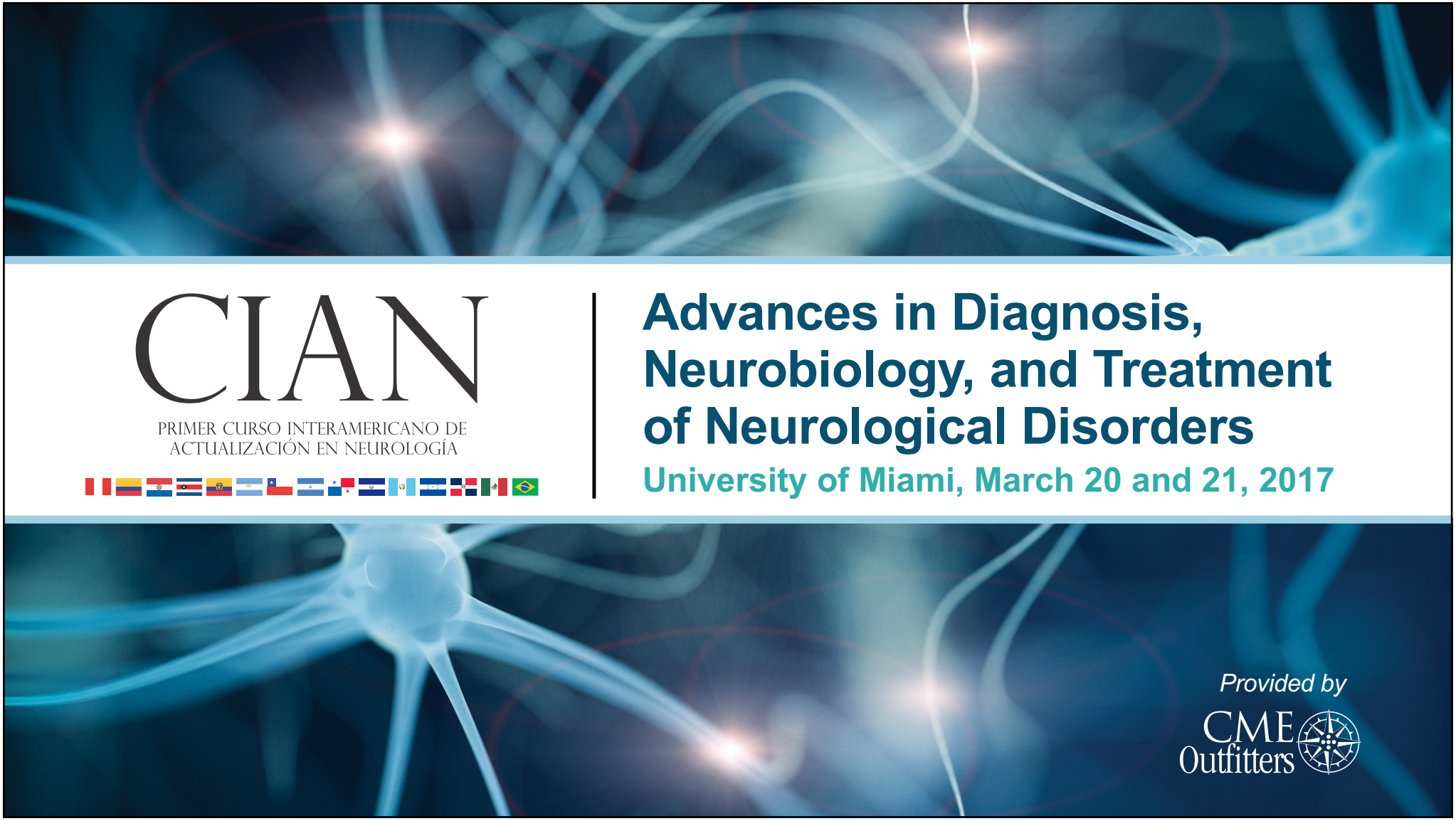

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PRIMER CURSO INTERAMERICANO DE ACTUALIZACIÓN EN NEUROLOGÍA

Advances in Diagnosis, Neurobiology, and Treatment of Neurological Disorders

University of Miami, March 20 and 21, 2017

Provided by

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Disclosures

- Dr. Sun has no disclosures to report.

Dementia:

Clinical and Management Advances and Collaborative Care Strategies Among Neurologists, Psychiatrists, and Other Specialists

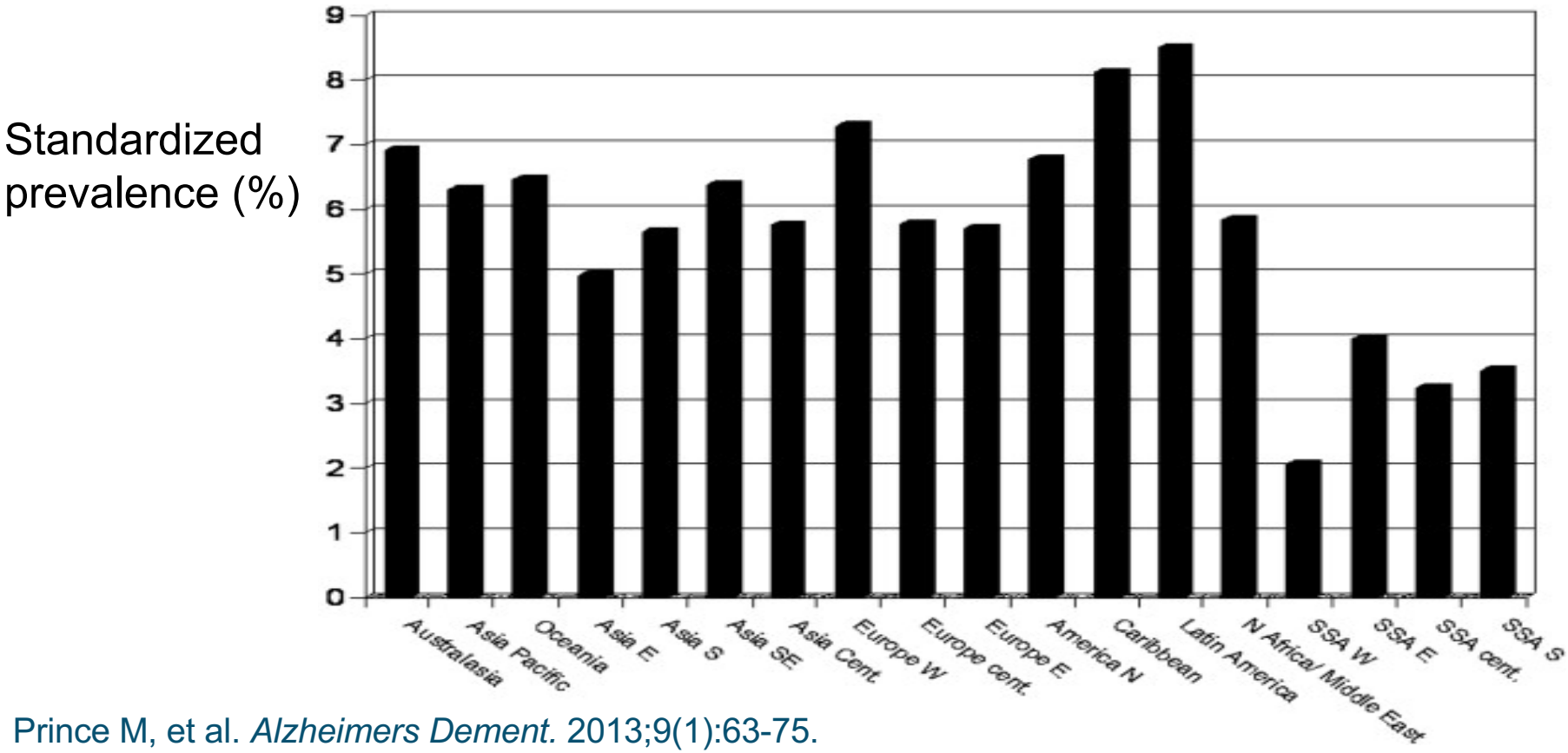
Learning Objective 1

Review the latest management advances and collaborative care strategies in dementia.

Outline

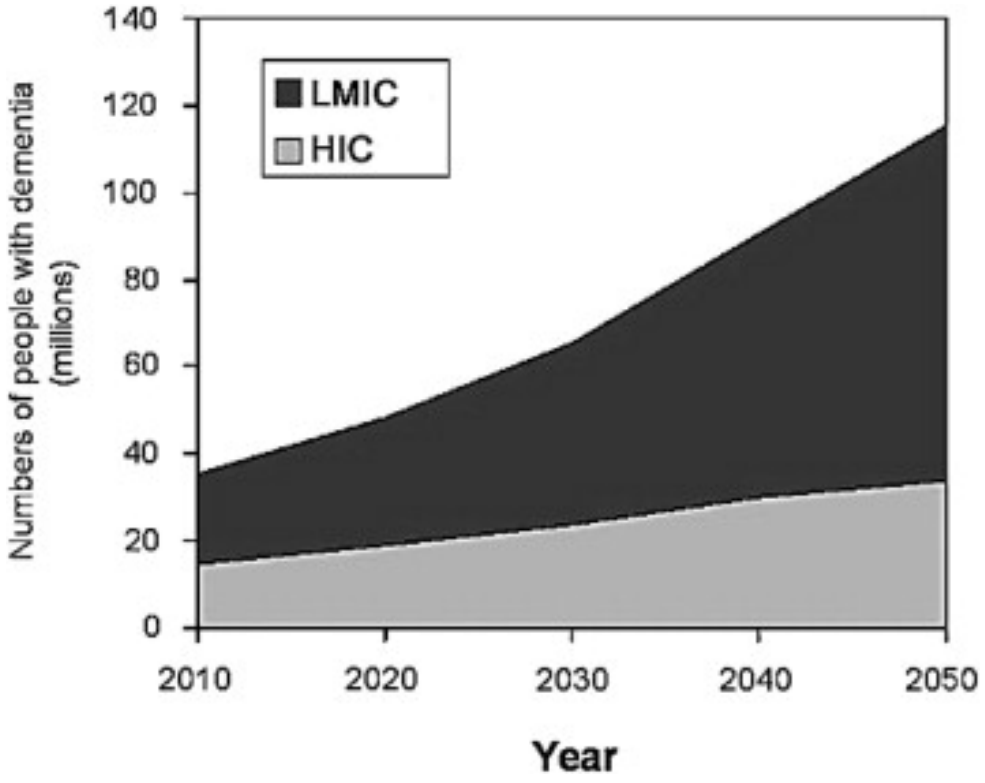
- Epidemiology of dementia
- Etiologies of dementia
- Recent developments in the diagnosis and management of neurodegenerative diseases
- Collaborative care strategies among neurologists, psychiatrists, and other specialists

Estimated Prevalence of Dementia for Those Aged > 60 Years Old



Prince M, et al. *Alzheimers Dement.* 2013;9(1):63-75.

Increase in Number of People With Dementia



Prince M, et al. *Alzheimers Dement*. 2013;9(1):63-75.

Etiologies of Dementia

Causes of Dementia	Types of Dementia
Degenerative diseases	AD, FTD, DLB, PSP, CBD, MSA
Vascular	Stroke-related, Vasculitis, CADASIL
Infectious	AIDS, Syphilis, CJD, herpes, Lyme's Disease, PML
Autoimmune/inflammatory	SLE, Sjogren's, MS, paraneoplastic
Tumors	Glioblastoma, lymphoma, metastatic tumors
Toxic/metabolic alcohol	B12 deficiency, thyroid, system failure
Traumatic	Closed head injury, CTE, anoxic brain injury
Psychiatric	Depression, anxiety, etc.
Hydrocephalus	
Other	

AD = Alzheimer's disease; FTD = frontotemporal dementia; DLB = Dementia Lewy Body; PSP = progressive supranuclear palsy; CBD = corticobasal dementia; MSA = multiple system atrophy; CADASIL = Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; CJD = Creutzfeldt–Jakob disease; PML = Progressive multifocal leukoencephalopathy; CTE = Chronic traumatic encephalopathy; AIDS = acquired immune deficiency syndrome; MS = multiple sclerosis.

Diagnosis

DSM-5 Criteria for Major Neurocognitive Disorder (Previously Dementia)
A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains*: - Learning and memory - Language - Executive function - Complex attention - Perceptual-motor - Social cognition
B. The cognitive deficits interfere with independence in everyday activities. At a minimum, assistance should be required with complex instrumental activities of daily living, such as paying bills or managing medications.
C. The cognitive deficits do not occur exclusively in the context of a delirium
D. The cognitive deficits are not better explained by another mental disorder (eg, major depressive disorder, schizophrenia)

American Psychiatric Association, American Psychiatric Association. *Diagnostic and statistical manual of mental disorders: DSM-5.* 5th ed. Washington, DC: American Psychiatric Association; 2013.

Clinical Assessment for Dementia

- Neurological examination
  - Mental status examination: cognitive deficits screened by office screening test including cognitive domains: attention, language, praxis, visual-spatial, abstract thinking, executive function, fluency, fund of knowledge
  - Behavioral and mood: apathy, depression, hallucinations
  - General neurological examination: any focal signs
- Imaging – CT or MRI, PET scan (FDG and special tracers)
- Laboratory – B-12 and thyroid function, FTA-ABS (Syphilis), HIV, autoimmune antibody screening, and Lyme disease
- Formal neuropsychological testing

FTA-ABS = fluorescent treponemal antibody absorption.

Mental Status Examination

Mini-Mental State Examination (MMSE)

Patient's Name: _____ Date: _____

Instructions: Score one point for each correct response within each question or activity.

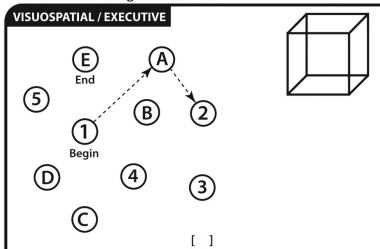
Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day? Month?"
5		"Where are we now? State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible.
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, ...) Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

MONTREAL COGNITIVE ASSESSMENT (MOCA)

Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE — POINTS



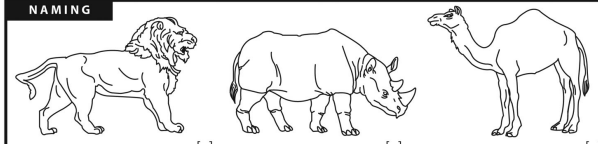
Copy cube

[ ] [ ]

Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands __/5

NAMING



[ ] [ ] [ ] __/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2 __/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B __/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** __/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ] __/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words) __/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler __/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City __/6

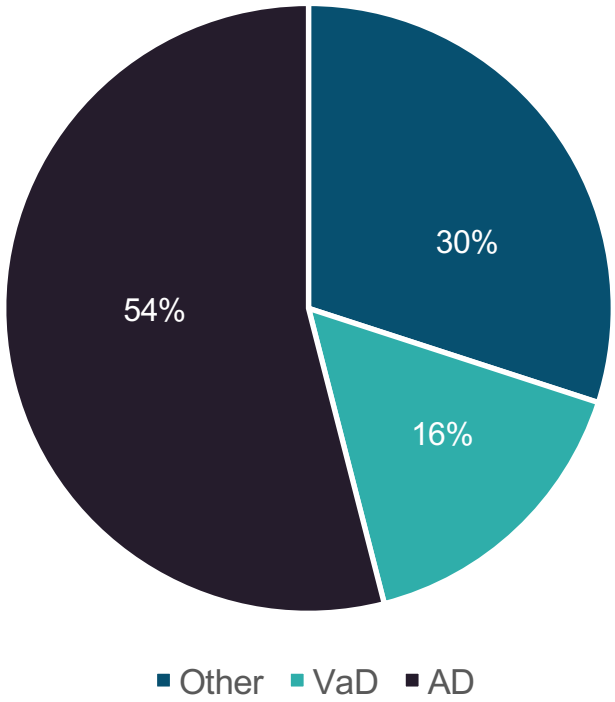
© Z.Nasreddine MD www.mocatest.org Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

Causes of Dementia With Late Onset (≥65 Years)

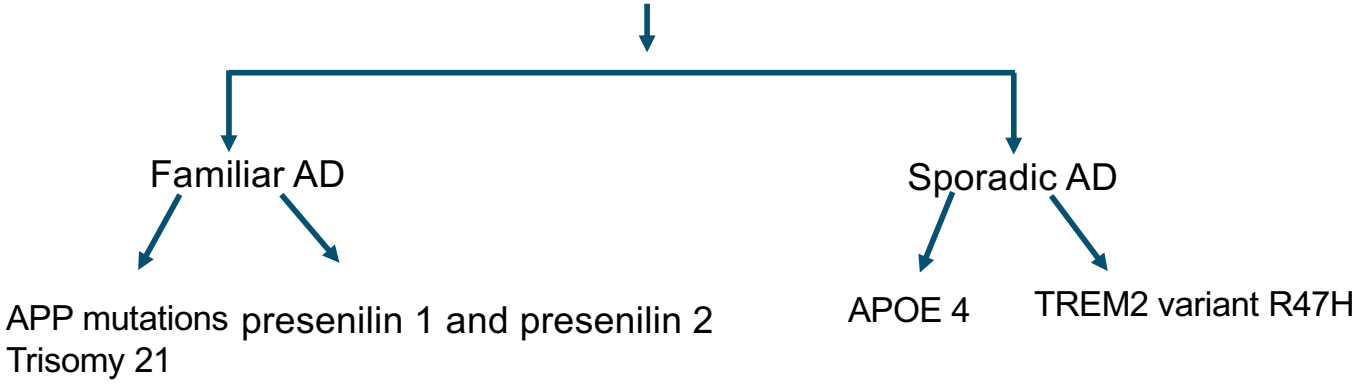


van der Flier VM, et al. *J Neurol Neurosurg Psychiatry*. 2005;76 Suppl 5:v2-v7.

Alzheimer's Disease Dementia

- Clinical syndrome arises as a consequence of the AD pathophysiological process
- Clinically classified as early onset of AD
- Pathologically, AD is composed of extracellular deposition of amyloid 42 and intracellular aggregation of hyper-phosphorylated tau protein

Genetics Alzheimer's Disease

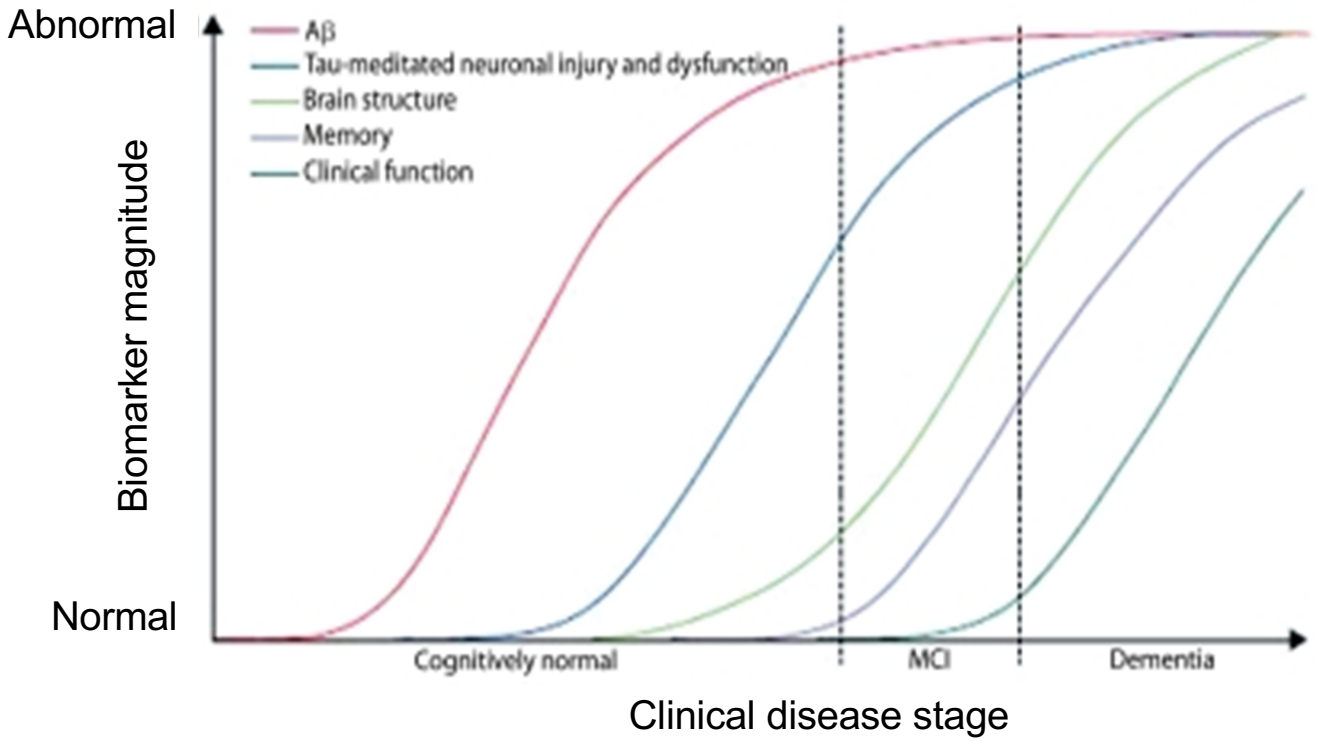


- A higher frequency of AD in Hispanic population compared to non-Hispanic white counterparts
- Earlier onset of symptoms in the Hispanic population compared to Caucasians
- the occurrence of the E4 allele in *APOE* is lower (38% in Hispanics AD cases, 59% in Caucasian AD cases)

Triggering receptor expressed on myeloid cells 2 (TREM2) rare variant R47H

Guerreiro R, et al. *N Engl J Med*. 2013;368(2):117-127;
Ravenscroft TA, et al. *Am J Neurodegener Dis.* 2016;5(1):94-101.

Clinical Course of Alzheimer's Disease



Jack CR, Jr. *Radiology*. 2012;263(2):344-361.

Probable AD

- Established diagnosis of dementia
  - Insidious onset
  - Progressive worsening of cognition by report or observation; and
  - The initial and most prominent cognitive deficits are evident on history or examination in one of the following:
    - Amnestic presentation:
      - Most common syndromic presentation of AD dementia
      - There should also be evidence of cognitive dysfunction in at least one other cognitive domain
    - Non-amnestic presentations
      - Language presentation (most prominent deficits are in word-finding)
      - Visuospatial presentation
      - Executive dysfunction

McKhann GM, et al. *Alzheimers Dement*. 2011;7(3)263-269.

Possible Alzheimer's Disease

- Dementia syndrome in the presence of variation in onset, presentation or clinical course of the disease
- Etiologically mixed presentation
  - Concomitant cerebrovascular disease or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or
  - Features of Dementia with Lewy bodies other than the dementia itself; or
  - Evidence for another neurological disease or a non-neurological medical comorbidity or medication use that could have a substantial effect on cognition

McKhann GM, et al. *Alzheimers Dement*. 2011;7(3)263-269.

Clinical Work-up

- Laboratory studies: CBC, CMP, B12 and Thyroid, RPR, and HIV
- Formal neuropsychological testing
- Brain imaging: MRI and FDG-PET scan
- Amyloid PET scan
- CSF study
  - Amyloid-42 ↓
  - Tau protein ↑

CBC = complete blood count; CMP = comprehensive metabolic panel; RPR = Rapid plasma reagin; FDG-PET = fluorodeoxyglucose positron emission tomography.

KR, et al. *Expert Rev Neurother*. 2007;7(4):407-422.

Vascular Dementia

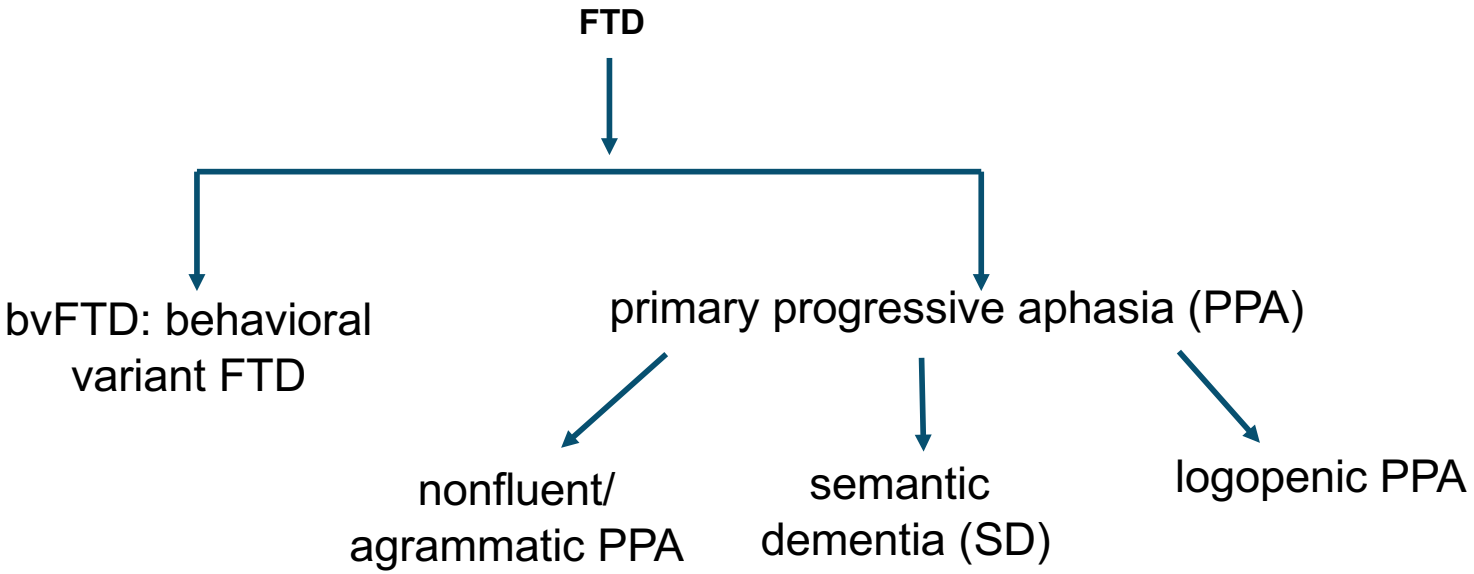
- Dementia or cognitive change with a cerebral vascular pathology
- Post-strokes dementia &/or radiologic evidence of cerebral infarcts
- Motor dysfunction including gait disorder and cognitive impairment at different domains such as dysexecutive function and slow processing speed
- Urinary incontinence may be prominent

Frontotemporal Dementia

- A heterogeneous disorder characterized by disturbances in behavior, personality and language accompanied by focal degeneration of the frontal and/or temporal lobes.
- Onset: often before 65 years, mean age of onset 58 years old
- Genetic factors:
  - C9ORF72, chromosome 9
  - MAPT, chromosome 17
  - GRN, chromosome 17

MAPT = microtubule associated protein tau; GRN = granulin precursor.

Types of Frontotemporal Dementia



Cortical Basal Degeneration

- A progressive asymmetric movement disorder
- Various combinations of akinesia, rigidity, dystonia, focal myoclonus, ideomotor apraxia, and alien-limb phenomena
- Asymmetric frontoparietal atrophy with extensive neuronal loss, gliosis, and ballooned achromatic neurons; Tau-positive astrocytic plaques are presently considered highly suggestive of CBD, as are tau inclusions in the glia

Progressive Supranuclear Palsy

- Progressive supranuclear ophthalmoplegia, gait disorder and postural instability, dysarthria, dysphagia, rigidity, and frontal cognitive disturbance
- The radiologic hummingbird sign
- The histologic characteristics of PSP include neuronal loss, gliosis, and the presence of tau-positive filamentous inclusions in specific anatomic areas

Dementia With Lewy bodies

- A neurodegenerative disease characterized by the presence of cortical Lewy bodies mainly composed of alpha-synuclein
- Part of a spectrum with Parkinson's disease, which has brainstem Lewy bodies.

McKeith I. *Dialogues Clin Neurosci*. 2004;6(3):333-341.

Diagnosis of DLB

- Progressive cognitive decline interferences with social and occupational functioning
- Deficit on tests of attention, executive function and visuospatial functioning is often prominent
- Prominent or persistent memory impairment may not be present early in the course of disease

McKeith I. *Dialogues Clin Neurosci*. 2004;6(3):333-341.

Diagnosis of DLB

- Two of the following core features are needed to make a diagnosis
  1. Fluctuating cognition
  2. Recurrent visual hallucination
  3. Parkinsonism
- Suggestive features: REM sleep behavioral disorder, severe neuroleptic sensitivity, low dopamine transporter uptake in basal ganglia
- Supportive features: falls, syncope, transient loss of consciousness, severe autonomic dysfunction, tactile or olfactory hallucination

REM = random eye movement.

McKeith I. *Dialogues Clin Neurosci*. 2004;6(3):333-341.

Chronic Traumatic Encephalopathy

- A progressive neurodegenerative disease that occurs in association with repetitive traumatic brain injury experienced in sport and military service.
- Core clinical features of traumatic encephalopathy syndrome
  - At least one of the core clinical features must be present:
  - Cognitive: Difficulties in cognition at a level of at least 1.5 standard deviations below appropriate norms.
  - Behavioral: Being described as emotionally explosive, physically violent, and/or verbally violent
  - Mood: Feeling overly sad, depressed, and/or hopeless

Montenigro PH, et al. *Alzheimers Res Ther*. 2014;6(5):68.

Supportive Features of Traumatic Encephalopathy Syndrome

- ✓ 1) Impulsivity
- ✓ 2) Anxiety
- ✓ 3) Apathy
- ✓ 4) Paranoia
- ✓ 5) Suicidality
- ✓ 6) Headache
- ✓ 7) Motor signs
- ✓ Documented decline
- ✓ 9) Delayed onset

Proposed Diagnosis of Traumatic Encephalopathy Syndrome

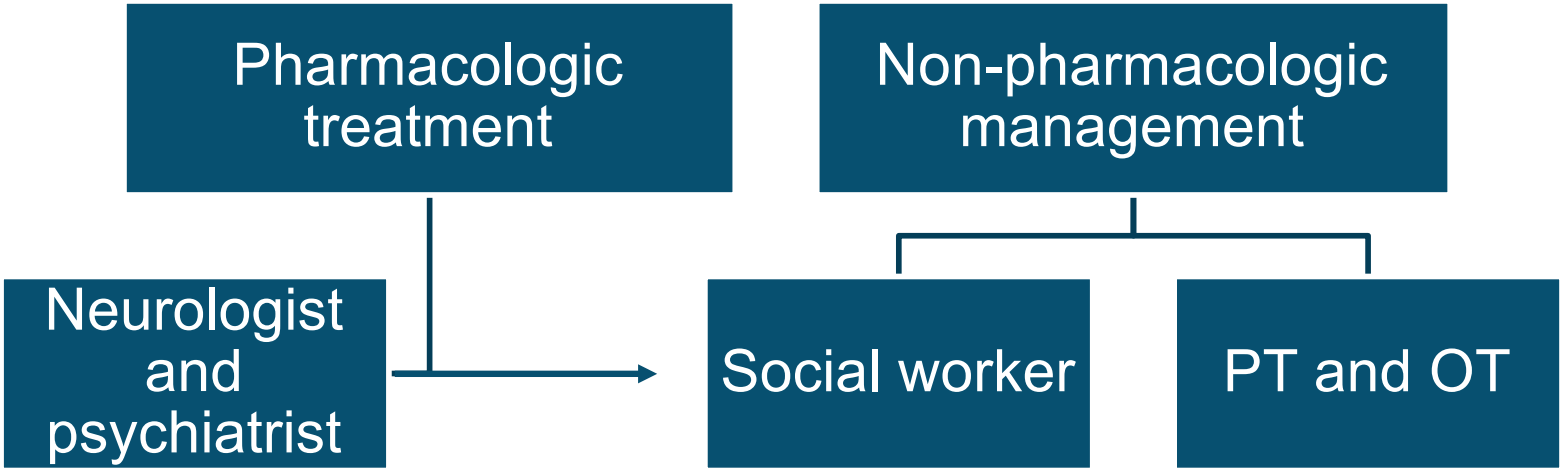
All five criteria must be met for a diagnosis of TES:

1. History of multiple impacts to the head
2. No other neurological disorders, mood/anxiety disorders, or other neurodegenerative diseases.
3. Clinical features must be present for a minimum of 12 months.
4. At least one of the core clinical features must be present and should be considered a change from baseline functioning.
5. At least two supportive features must be present.

Montenigro PH, et al. *Alzheimers Res Ther*. 2014;6(5):68.

Management of Dementia

Memory Disorder Clinic
Pharmacological and Non-Pharmacological Approach



Pharmacological Management

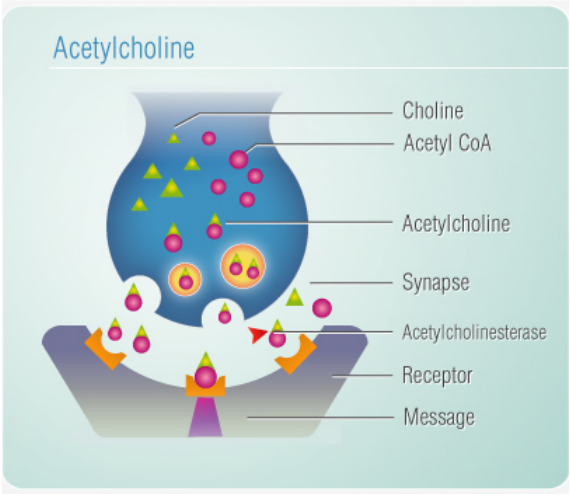
- Positive management
- Accurate diagnosis
- Understanding pathophysiology
- Medications
  - Cholinesterase inhibitors
  - NMDA receptor antagonist

Medications

- Donepezil
  - 5 mg daily for one month and titrate up 10 mg po daily as tolerate
  - Mild, moderate and severe; less side-effect
- Rivastigmine
  - Oral: 1.5 mg, twice a day for one month; then 3 mg twice a day; GI symptoms
  - Patch: 4.6 mg/5 cm2 over 24 hrs; 9.5 mg/10 cm^2 over 24 hrs; rush
- Galantamine
  - 8 mg/day for one month; then 16 mg/day dose
  - Usually, at least two months (after starting at effective dose) are needed to know whether the drug is meeting the goals of treatment.

The Function of Cholinesterase Inhibitors (ChEIs) in Treating Alzheimer's Disease (AD)

1. Acetyl CoA and Choline join
2. Acetylcholine is formed
3. Acetylcholine is packaged up to leave the axon
4. Acetylcholine leaves the neuron and begins to cross the synapse
5. Acetylcholine reaches the other side of the synapse and binds to the receptor causing the message to be sent
6. After the message is sent, Acetylcholine is released into the synapse
7. Acetylcholinesterase breaks down Acetylcholine, inactivating it



Cholinesterase Inhibitors

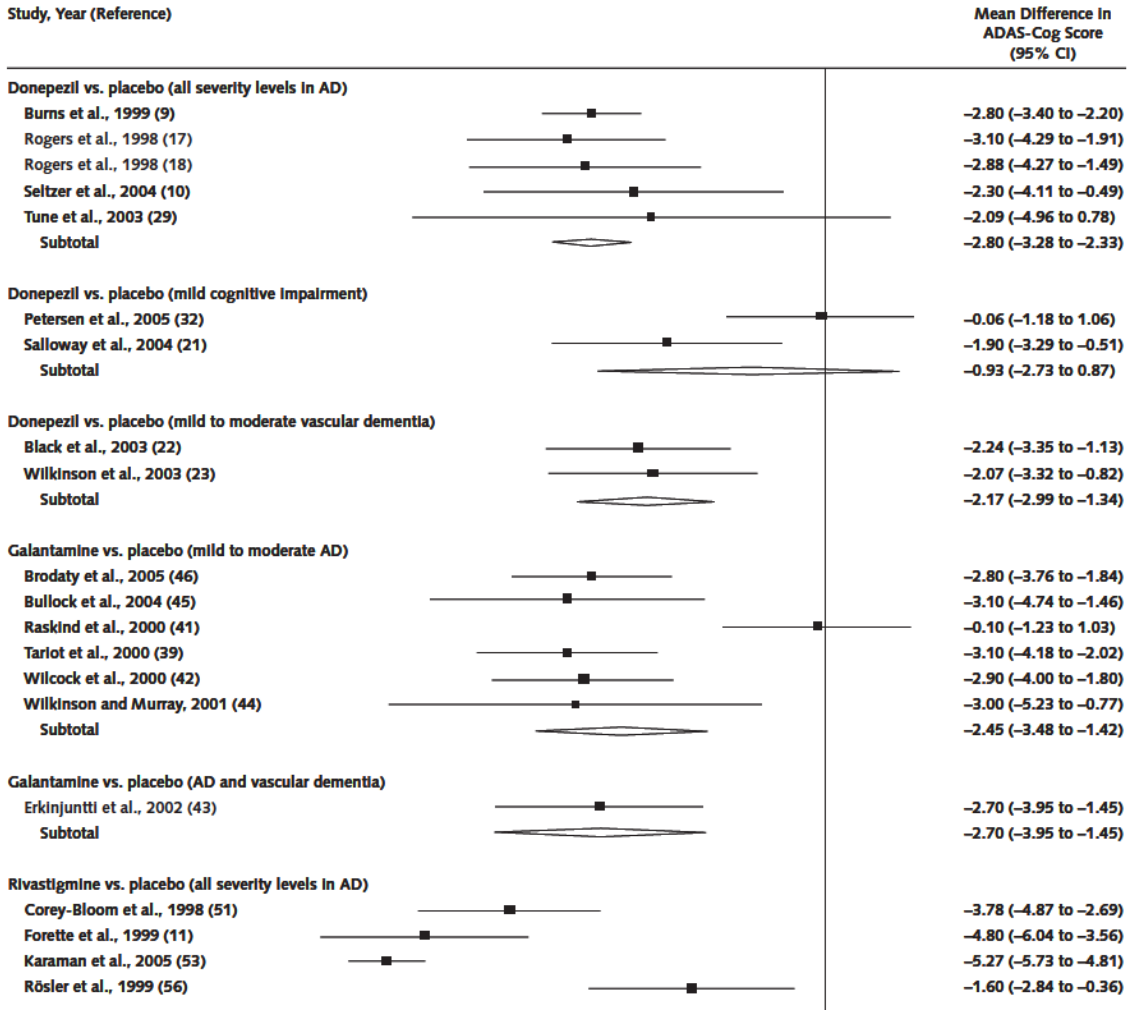
- Improve cognition, participation in activities of daily living and global function in mild to moderate disease
- Improve cognition and behavior in mild to moderate and moderate to severe disease
- Reduce emergent behavioral disturbance in mild to moderate disease

Side Effects of Cholinesterase Inhibitors

- GI, anorexia, nausea/vomiting/diarrhea 20%
- Vivid dreams
- Increased salivation
- Increased rhinorrhea
- Muscle cramps
- Rarely slows heart rate; 3%
- Others

GI = gastrointestinal.

Summary of Beneficial Effect of Cholinesterase Inhibitors



Raina P, et al. *Ann Intern Med*. 2008;148(5):379-397.

NMDA Receptor Antagonist

- Memantine (Noojerone) is a low-affinity noncompetitive antagonist of the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptors (GluR).

Dysfunction of Glutamatergic Signaling

- Glutamate is responsible for approximately 70% of the excitatory neurotransmission in the central nervous system (CNS), particularly in the cortical and hippocampal regions
- In AD, research studies show NMDA receptors are constantly over-activated, leading to sustained Ca2 influx, resulting in neuron injury

Combination Therapy

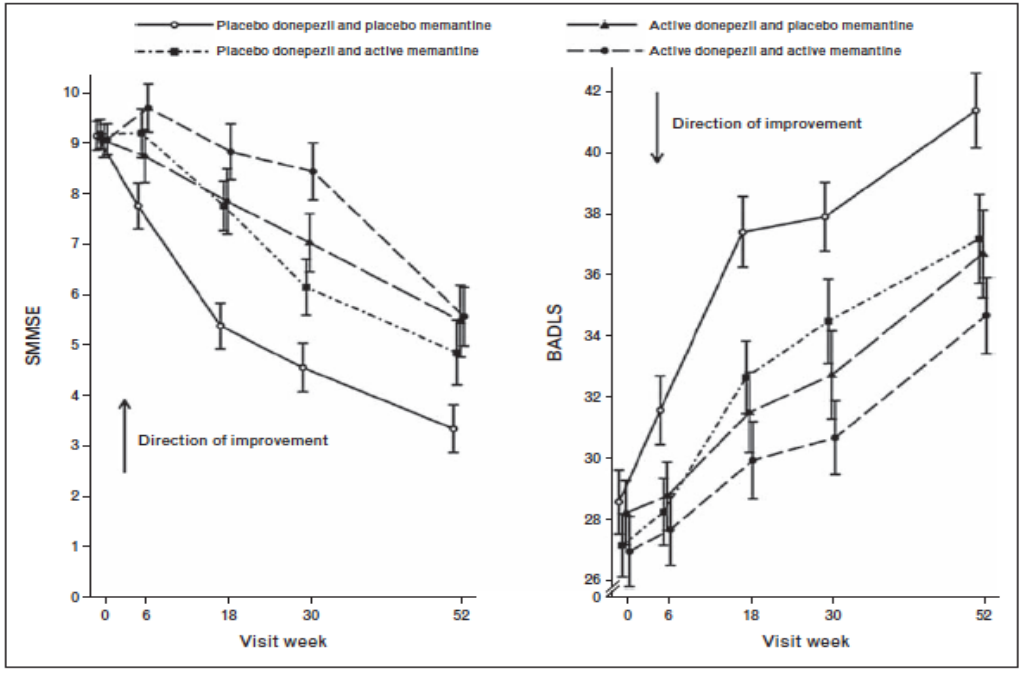


FIGURE 1. Donepezil and memantine for moderate to severe Alzheimer's disease. Mean scores and standard errors on the Standardized Mini-Mental State Examination and the Bristol Activities of Daily Living Scale according to visit week and four different treatment groups after discontinuation of donepezil. BADLS, Bristol Activities of Daily Living Scale; SMMSE, Standardized Mini-Mental State Examination. Reprinted with permission [4**].

Howard, R et al. *N Engl J Med*. 2012;366:893-903.

Treatment Expectations

- Small but noticeable improvements
- Less time spent looking for keys, glasses
- Repeats self less often
- Dwells in past less
- Easier time keeping track of conversation
- More engaged, outgoing

Management of Neuropsychiatric Symptoms

- Psychosis and agitation
  - Short-term atypical antipsychotic drugs such as quetiapine and risperidone
  - No haloperidol
  - SSRIs (sertraline, trazodone)
- Depression
  - Sertraline

Non-Pharmacologic Treatment

- Traditional cognitive training
  - Small effect size in the early stages of AD
  - Psycho-social intervention for OT supervised life modification
- Computer-based cognitive training
- Social worker evaluation
- Driving safety

Future Directions

Summary

- Dementia is a serious public health issue in an aging society.
- Alzheimer's disease is the most common form of dementia among people aged above 65 years old.
- Positive collaborative management includes pharmacological and non-pharmacological treatment.

Questions & Answers

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