

## Management of Cognitive Impairment: *Pharmacologic and Non-Pharmacologic Therapies*

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## Outline

- ❖ Definition of Dementia
  - Etiologies
  - Severity
- ❖ Principles of Dementia Management
  - Manage Cognitive Status
  - Manage Functional Status
- ❖ Pharmacotherapy for Dementia
  - Cholinesterase Inhibitors
  - Memantine
  - Vitamin E
  - Drugs in the Pipeline
- ❖ Non-pharmacologic Management of Dementia
  - Body
  - Mind
  - Friends

## Mr. J

- ❖ 83 y.o. M with hx of CAD, HTN, HLD, CLL, BPH and RA. Seeing you in primary care clinic for routine follow up.
- ❖ Wife accompanies him, says she wants to talk about memory; she shares that patient is struggling with short term memory and word finding. Has gotten lost in WalMart and has gotten lost driving around the neighborhood.
- ❖ Patient and wife want to know what's going on and what they should do to stop it.

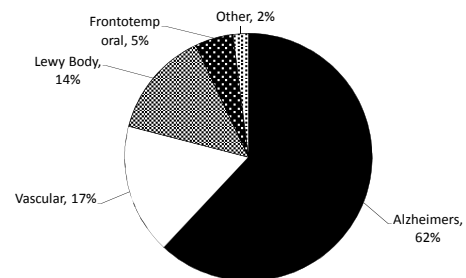
## Ms. G

- ❖ 77 y.o. F with hx of DM, HTN, HLD, CAD, cerebral aneurysm s/p clipping and moderate dementia (MoCA 13) presents to your primary care practice as a new patient.
- ❖ She has been on rivastigmine and donepezil in the past, but couldn't tolerate them due to side effects including abdominal pain, nausea and muscle aches.
- ❖ Her caregivers want to know if there are other medications to use to treat her dementia.
- ❖ Her caregivers also tell you she is yelling, hitting, and threatening her housemates. They wonder what they can do about her behaviors.

## Definition of Dementia

- ❖ Major Neurocognitive Disorder:
  - Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains...The cognitive deficits interfere with independence in everyday activities...(APA:DSM V)

## Dementia Prevalence



(AGS: Geriatrics Review Syllabus) (Alzheimer's Association: [www.alz.org](http://www.alz.org), 2013)

# Alzheimer's Dementia

**SYMPTOMS:**

- Difficulty communicating
- Agitation and mood swings
- Difficulty with familiar tasks
- Confusion with time or place
- Trouble planning or problem solving
- Trouble with visual or spatial relationships
- Seemingly purposeless activity
- Misplacing judgment
- Verbal and physical aggression
- Trouble recognizing family and friends
- Loss of initiative and motivation
- Inappropriate behavior
- Loss of motor skills and sense of touch
- Disregard for grooming and hygiene
- Repetitive speech or actions
- Delusions and paranoia

Wandering  
Withdrawal  
Trouble sleeping  
Memory loss

Most common form of dementia that causes problems with memory, thinking, and behavior.

# Vascular Dementia

**Diagnostic criteria:**

- Decreased cognition in 2 or more areas
- Temporal relation of vascular and neurologic symptoms
- Evidence of cerebrovascular disease

**Other clinical findings include:**

- Hypertension
- Cardiovascular and/or renal disease
- Focal neurologic signs

**Cerebrovascular disease results in multiple small cortical and subcortical infarcts.**

**Disease progression (years):** Shows a stepwise decline in cognitive function over time.

**Clinical progression:** Vascular dementia exhibits abrupt onset and stepwise progression in contrast to gradual onset and progression of Alzheimer disease.

Most patients with vascular dementia have increased risk factors for stroke.

(Image: Budson & Solomon, Memory Loss. 2011)

# Dementia with Lewy Bodies

**Dementia With Lewy Bodies:**

- Marked fluctuations in attention
- Rigidity and slowed movement
- Visual hallucinations are hallmark finding
- Short shuffling gait
- Patients exhibit parkinsonian motor disturbances
- Cortical Lewy bodies plus loss of dopamine projections to frontal cortex and basal ganglia results in dementia
- Lewy body
- Neuron
- Dopamine Normal
- Dopamine
- Lewy body dementia
- Lewy bodies are found in substantia nigra as well as other brainstem nuclei and cortex.

(Image: Budson & Solomon, Memory Loss. 2011)

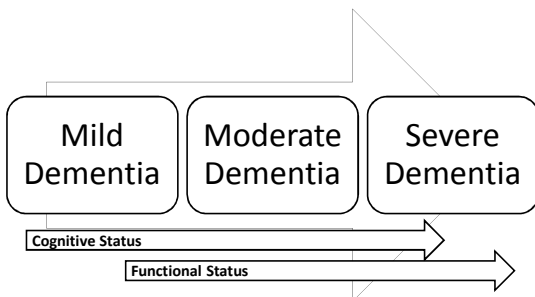
# Frontotemporal Dementia

**Frontotemporal Dementia:**

- Circuitry in frontal lobe variant
- Decrease in speech
- Loss of awareness of emotions and hygiene
- Bizarre, uninhibited socially inappropriate behavior
- Old habits: increased eating, excess weight gain
- Decreased concern and empathy for others

(Image: Budson & Solomon, Memory Loss. 2011)

# Severity of Dementia



# Principles of Dementia Management

- ❖ Cognitive Status
- ❖ Functional Status

## Cognitive Status

Measure	Manage
<ul style="list-style-type: none"> <li>❖ Brief Cognitive Screening Instruments:                             <ul style="list-style-type: none"> <li>▪ MoCA</li> <li>▪ MMSE</li> </ul> </li> <li>❖ Research Study Tools:                             <ul style="list-style-type: none"> <li>▪ ADAS-cog</li> <li>▪ Clinician's Global Impression of Change</li> <li>▪ MMSE</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>❖ Patient and Caregiver Education                             <ul style="list-style-type: none"> <li>▪ Patient Expectations</li> <li>▪ Caregiver and Family Expectations</li> </ul> </li> <li>❖ Address the Rate of Cognitive Decline</li> <li>❖ Manage Co-Morbid Mood Disorders</li> <li>❖ Address Behavioral Disturbances</li> </ul>

## Functional Status

Measure	Manage
<ul style="list-style-type: none"> <li>❖ Activities of Daily Living</li> <li>❖ Instrumental Activities of Daily Living</li> <li>❖ Entry into Institutional Care</li> <li>❖ Research Study Tools:                             <ul style="list-style-type: none"> <li>▪ BADLS</li> <li>▪ Functional Rating Scale</li> <li>▪ Disability Assessment</li> <li>▪ Caregiver Burden Tools</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>❖ Patient Safety:                             <ul style="list-style-type: none"> <li>▪ Physical Safety</li> <li>▪ Advanced Care Planning</li> <li>▪ Fraud Prevention</li> </ul> </li> <li>❖ Assess Living Situation</li> <li>❖ Support Caregivers</li> </ul>

## Pharmacotherapy of Dementia

## Cholinesterase Inhibitors: Basics

### Drugs:

Donepezil  
Galantamine  
Rivastigmine

### Dementia

Reduced Cortical Cholinergic Function

### Adverse Effects:

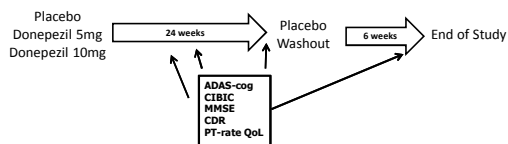
Cholinergic Effects  
• GI Distress  
• Headaches  
• Bradycardia\*

### Cholinesterase Inhibitors

Increased Cholinergic Transmission in Synaptic Cleft

## Cholinesterase Inhibitors: Evidence in Alzheimer's Dementia

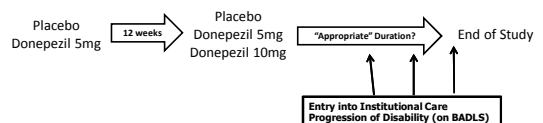
- ❖ Donepezil
  - 24-Week Double Blind Placebo Controlled RCT, 1998
  - 473 Patients with Mild to Moderate Alzheimer's Dementia
  - Drug-Company Funded: Eisai Inc., makers of Aricept



(Neurology 1998; 50:136)

## Cholinesterase Inhibitors: Evidence in Alzheimer's Dementia

- ❖ Donepezil
  - Double Blind Placebo Controlled RCT, 2004: "AD2000"
  - 565 Patients with Mild to Moderate Alzheimer's Dementia
  - Community-Dwelling patients, Referred to Memory Clinic
  - NOT Drug-company funded
  - Designed to look at longer-term use of donepezil



(Lancet 2004; 363: 2105-15)

## Cholinesterase Inhibitors: Evidence in Alzheimer's Dementia

### Cochrane Review: Donepezil for Dementia due to Alzheimer's Disease (2009)

- ❖ Meta-Analysis of 24 RCTs: Placebo vs. Donepezil
- ❖ 5796 Patients with Mild, Moderate or Severe AD.
- ❖ Donepezil (5mg or 10mg daily) at 24 Weeks:
  - Statistically significant improvement on the ADAS-Cog.
  - Statistically significant improvement in Global Clinical State.
  - Statistically significant improvement in ADLs.
  - Statistically significant improvement in Behavior.
  - No improvement in Quality of Life measures.
- ❖ More people withdrew from studies on 10mg dose than 5mg.
- ❖ Benefits were marginally larger for 10mg dose than 5mg.

## Cholinesterase Inhibitors: Evidence in Alzheimer's Dementia

- ❖ Galantamine
  - Multiple RCTs for AD
  - Effective in Mild to Moderate AD
    - Slows decline in cognition.
    - Slows decline in ADLs.
- ❖ Rivastigmine
  - Evaluated in Multiple RCTs for AD, Vasc Dementia
  - Effective in Mild to Moderate AD
  - Cochrane Review Meta-Analysis of 13 Trials in 2015 for AD:
    - Overall improvement Rivastigmine vs. placebo: OR 1.47 (1.25- 1.72).
    - Patch 9.5mg/day had reduced side effects compared to 6-12mg PO daily.
  - Similar Results when Compared to Donepezil.
- ❖ Head to Head Comparisons of CI's
  - NONE

## Cholinesterase Inhibitors: Evidence in Non-AD Dementias

### Evidence of Benefit?

Drug	AD	Vasc D	Mixed	PD	FTD	MCI	TBI
Donepezil	Yes	Yes		Yes	No	No	
Galantamine	Yes	Yes	Yes		No	No	
Rivastigmine	Yes	Yes	Yes	Yes	No	No	No

Blank = no data

## Memantine (Namenda): Basics

### Drugs:

Memantine  
Dose: 10mg BID  
Taper up

### Dementia

Cortical and Hippocampal Neurons Susceptible to Damage from Glutamate Excitation at the NMDA Receptor

### Adverse Effects:

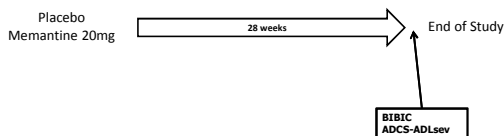
Very Few Reported!  
• Dizziness  
• Confusion  
• Hallucinations

### NMDA Receptor Antagonist

Protect Neurons from Damage and Improve Neuronal Function

## Memantine (Namenda): Evidence in Alzheimer's Dementia

- ❖ 28 Week Double Blind RCT, 2003
- ❖ 252 Patients with Moderate-Severe AD (MMSE 3-14)



(NEJM. 2003; 348(14):1333)

## Memantine (Namenda): Evidence in Vascular Dementia

- ❖ 2 RCTs, Both 28 Weeks
- ❖ Patients with Mild-Moderate Vascular Dementia
- ❖ Memantine 20mg vs. Placebo:
  - Benefit on cognitive scales: ~ 2pts on ADAS-cog.
  - No benefit on global impression of change.
  - No benefit on ADLs.
  - Rate of adverse events ~ placebo in both studies.

(Stroke. 2002;33(7):1834) (Int Clin Psychopharmacol. 2002;17(6):297)

## Cholinesterase Inhibitors + Memantine

❖ 24 Weeks RTC, 322 Patients, Mod-Severe AD:

Donepezil + Memantine

- Donepezil + Placebo

Better Cognitive Scores  
Better ADL Scores  
Better Global Outcome  
Better Behavior

(JAMA 2004; 291:317)

## Vitamin E: Basics

### Drugs:

Vitamin E (alpha tocopherol)  
2000 IU Daily

### Dementia

Cortical Neurons Susceptible to Damage from Oxidative Stress

### Adverse Effects:

High Dose → Mortality  
High Dose → Heart Failure  
Low Dose → Very Few Issues

### Antioxidant

Protect Cortical Neurons from Damage

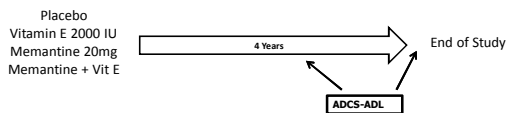
## Vitamin E: Evidence in Alzheimer's Dementia

❖ 4 Year Double Blind RCT:

- Vit E vs Memantine vs. Combo vs. Placebo.
- "VA TEAM-AD Study".

❖ 613 Patients from the VA with Mild-Moderate AD;  
97% male

❖ Only 58% of Participants Completed 4 Year Study Protocol



(NEJM. 2003; 348(14):1333)

## Pharmacologic Management: Limitations of the Evidence

- ❖ Most Studies Only Look at AD
  - Inconsistent definition of diagnostic criteria.
  - Inconsistent definition of severity.
- ❖ Recruitment and Retention of Participants can be Very Difficult
  - Consent issues.
  - Challenges contacting patients.
- ❖ Heterogeneous Outcome Measures
  - Vary with disease severity.
- ❖ Differences Between Drug-Company Study Populations and the "Real World"

## Controversies in Pharmacologic Management of Dementia

❖ When to Stop Dementia Meds?

- Duration of clinical trials:
  - 24 weeks, 28 weeks, 2 years, 4 years.

❖ Duration of Effect After Discontinuation?

- None with CI's.
- Some with Memantine?

❖ Cognitive Loss with Stopping Meds?

- Reversibility with resumption?

❖ Applicability Across Care Settings

- Independent living vs. ALF vs. SNF.

## Exciting Things in the Pipeline:

❖ Insulin, Intranasal

- Insulin mitigates beta amyloid deposition.
- Insulin mitigates phosphorylation of tau.
- Restoration of brain insulin signaling → very promising.

❖ MPL (Monophosphoryl Lipid A)

- TLR-4 Agonist derived from lipopolysaccharides.
- Stimulates the immune system to remove amyloid beta.
- Significant reduction in amyloid beta load in mice.
- Enhanced cognitive function in mice.
- Exciting because it is potentially disease modifying!

(Front Neurosci. 2015 Jun 16;9:204) (Proc Natl Acad Sci U S A. 2013 Jan 29;110(5):1941-6)

## Non-Pharmacologic Management of Dementia

## Physical Exercise

- ❖ RCTs of Structured Exercise Programs in Community-Dwelling and SNF Patients with Mild-Severe AD:
  - No improvement in cognitive function.
  - Improvement in physical function.
  - Slower rate of functional decline.
  - Improvement in neuropsychiatric symptoms and depression.
- ❖ Mounting Evidence for Structured Exercise to Prevent Dementia in Healthy Older Adults or Older Adults with MCI
  - Improvement in cognitive function in MCI.

(JAMA 2003; 290:2015) (JAMA Intern Med 2013; 173:894) (Arch Neurol. 2010 Jan;67(1):71-9)

## Mental Stimulation

- ❖ Cognitive Stimulation Programs Probably Benefit Cognition, BUT:
  - Highly variable techniques – lack of standardization.
  - Highly variable study quality.
  - Heterogeneous study populations.
- ❖ Cognitive Rehabilitation Can Help Patients:
  - Develop strategies to compensate for memory loss.
  - Maintain memory in early stages.
  - Provide caregiver/family education and support.

## Social Networks and Generativity

- ❖ Enjoyable Leisure Activities Can:
  - Slow memory loss in pts with Dementia or MCI.
  - Reduce neuropsychiatric symptoms in pts with Dementia.
  - Improve Functional Capacity.
- ❖ Cognitive Improvements in “Enriched Environments”

(Prog. Neurobiol. 89; 369-382)

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## Questions

