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

83yo 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 pt is struggling with short term memory and word finding. Has gotten lost in WalMart and has gotten lost driving around the neighborhood.

Pt and wife want to know what's going on and what they should do to stop it.
Ms. G

- 77yo 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

Etiologies

Severity

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

- Alzheimer's: 62%
- Vascular: 17%
- Lewy Body: 14%
- Frontotemporal: 5%
- Other: 2%

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

Alzheimer's Dementia

- Memory
- Confusion
- Expressive aphasia
- Loss of judgment
- Agitation
- Aggression
- Agapathic behavior
- Atrophy or amnestic syndrome
- Personality change
- Depression
- Delusions
- Hallucinations
- Agitation
- Anxiety
- Sleep disturbances
- Emotions

Vascular Dementia

- Memory
- Confusion
- Expressive aphasia
- Loss of judgment
- Agitation
- Aggression
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- Atrophy or amnestic syndrome
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(Budson & Solomon, Memory Loss, 2011)
Dementia with Lewy Bodies

Frontotemporal Dementia

Severity of Dementia
# Principles of Dementia Management

## Cognitive Status

**Measure**
- Brief Cognitive Screening Instruments:
  - MoCA
  - MMSE
- Research Study Tools:
  - ADAS-cog
  - Clinician’s Global Impression of Change
  - MMSE

**Manage**
- Patient and Caregiver Education
- Patient Expectations
- Caregiver and Family Expectations
- Address the rate of Cognitive Decline
- Manage Co-morbid Mood Disorders
- Address Behavioral Disturbances

## Functional Status

**Measure**
- Activities of Daily Living
- Instrumental Activities of Daily Living
- Entry into Institutional Care
- Research Study Tools:
  - BADLS
  - Functional Rating Scale
  - Disability Assessment
  - Caregiver Burden Tools

**Manage**
- Patient Safety:
  - Physical Safety
  - Advanced Care Planning
  - Fraud Prevention
- Assess Living Situation
- Support Caregivers

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**Brief Cognitive Screening Instruments:** MoCA, MMSE

**Research Study Tools:** ADAS-cog, Clinician’s Global Impression of Change, MMSE

**Patient and Caregiver Education**

**Patient Expectations**

**Caregiver and Family Expectations**

**Address the rate of Cognitive Decline**

**Manage Co-morbid Mood Disorders**

**Address Behavioral Disturbances**

**Activities of Daily Living**

**Instrumental Activities of Daily Living**

**Entry into Institutional Care**

**BADLS**

**Functional Rating Scale**

**Disability Assessment**

**Caregiver Burden Tools**

**Patient Safety:** Physical Safety, Advanced Care Planning, Fraud Prevention

**Assess Living Situation**

**Support Caregivers**
Pharmacotherapy Of Dementia

Cholinesterase Inhibitors: Basics

**Drugs:**
- Donepezil
- Galantamine
- Rivastigmine

**Adverse Effects:**
- Cholinergic Effects
- GI Distress
- Headaches
- Bradycardia

Increased Cholinergic Transmission in Synaptic Cleft

Reduced Cortical Cholinergic Function

Cholinesterase Inhibitors: Evidence in Alzheimer's Dementia

- **Donepezil**
  - 24wk double blind placebo controlled RCT: 1998
  - 473 pts with Mild to Moderate Alzheimer's Dementia
  - Drug-company funded: Eisai Inc., makers of Aricept

<table>
<thead>
<tr>
<th>Drug</th>
<th>Placebo Washout</th>
<th>24wks</th>
<th>6wks</th>
<th>End of Study</th>
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<tbody>
<tr>
<td>Placebo</td>
<td>Donepezil 5mg</td>
<td>Donepezil 10mg</td>
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**Endpoints:**
- ADAS-cog
- CIBIC
- MMSE
- CDR
- Pt-rate
- QoL

**Cholinesterase Inhibitors: Evidence in Alzheimer’s Dementia**

- **Donepezil**
  - Double blind placebo controlled RCT, 2004: “AD2000”
  - 565 pts 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

  ![Placebo vs. Donepezil Graph](image)

- **Cochrane Review:** Donepezil for dementia due to Alzheimer’s disease (2009)
  - Meta-analysis of 24 RCTs: placebo vs. donepezil
  - 5796 pts with mild, moderate or severe AD
  - Donepezil (5mg or 10mg daily) at 24wks:
    - Statistically significant improvement on the ADASCog
    - Statistically significant improvement in Global Clinical State
    - Statistically significant improvement in ADLs
    - 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

- **Galantamine**
  - Multiple RCTs for AD
  - Effective in mild to moderate AD
  - Slows decline in cognition

- **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 5-12mg PO daily
    - Similar results when compared to donepezil

- **Head to Head Comparisons of CIs**
  - NONE.
### Cholinesterase Inhibitors: Evidence in Non-AD Dementias

<table>
<thead>
<tr>
<th>Drug</th>
<th>AD</th>
<th>Vsc. D</th>
<th>Mixed</th>
<th>PD</th>
<th>FTD</th>
<th>MCI</th>
<th>TBI</th>
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<td>Donepezil</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Na</td>
<td>Na</td>
</tr>
<tr>
<td>Galantamine</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Na</td>
<td>Na</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Na</td>
<td>Na</td>
</tr>
</tbody>
</table>

Blank = no data

### Memantine (Namenda): Basics

**Drugs:** Memantine  
Dosage: 10mg BD  
Taper up

**Adverse Effects:**  
Very few reported!  
Dizziness  
Confusion  
Hallucinations

**NMDA Receptor Antagonist**  
Protect Neurons from Damage and Improve Neuronal Function

**Dementia**

Cortical & Hippocampal Neurons susceptible to Damage from Glutamate Excitation @the NMDA Receptor

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

- 28wk double blind RCT, 2003  
- 252pts with moderate-severe AD (MMSE 3-14)

Placebo Memantine 20mg  
28wk  
End of Study

NEJM. 2003; 348(14):1333.
Memantine (Namenda): Evidence in Vascular Dementia

- 2 RCTs, both 28wks
- Pts 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

Cholinesterase Inhibitors + Memantine

- 24wk RTC, 322pts, mod-severe AD:
  - Donepezil + Memantine
  - Donepezil + Placebo

Better Cognitive Scores
Better ADL Scores
Better Global Outcome
Better Behavior

Vitamin E: Basics

<table>
<thead>
<tr>
<th>Drug: Vitamin E [alpha tocopherol] 2000 IU daily</th>
</tr>
</thead>
</table>
| Adverse Effects: High dose → mortality
  High dose → heart failure
  Low dose - very few issues |

Antioxidant

Protect Cortical Neurons from Damage

Cortical Neurons susceptible to damage from Oxidative Stress
Vitamin E: Evidence in Alzheimer’s Dementia

- 4 year double blind RCT: Vitamin E vs Memantine vs. Combo vs. Placebo
  
  “VA TEAM AD Study”
- 613 pts from the VA with mild-moderate AD; 97% male
- Only 58% of participants completed 4yr study protocol

Placebo
Vitamin E 2000 IU
Memantine 20mg
Memantine + Vit E

End of Study

Pharmacologic Management: Limitations of the Evidence

- Most studies only look at AD
  - Inconsistent definition of diagnostic criteria
  - Inconsistent definition of severity
- Recruitment & 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, 28wks, 2yrs, 4yrs
  - Duration of effect after discontinuation?
    - None with CIs
    - 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!

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
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 & 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"

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References

- Alzheimer’s Assoc; Chicago, IL. www.alz.org; 2013.


Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER). ClinicalTrials.gov NCT01041989.

