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)
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

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

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
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
- 5,796 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.
  - 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.
- 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

Memantine (Namenda): Basics

Drugs:
- Memantine
  - Dose: 10mg BID
  - Taper up
- Cortical and Hippocampal Neurons Susceptible to Damage from Glutamate Excitation at the NMDA Receptor

Dementia
- NMDA Receptor Antagonist
- Protect Neurons from Damage and Improve Neuronal Function

Adverse Effects:
- Very Few Reported!
  - Dizziness
  - Confusion
  - Hallucinations

Memantine (Namenda): Evidence in Alzheimer’s Dementia

- 28 Week Double Blind RCT, 2003
- 252 Patients with Moderate-Severe AD (MMSE 3-14)
- Placebo
- Memantine 20mg
- 28 weeks
End of Study

End of Study

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.


Cholinesterase Inhibitors: Evidence in Alzheimer’s Dementia

Evidence of Benefit?

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<th>Drug</th>
<th>AD</th>
<th>Vasc D</th>
<th>Mixed</th>
<th>PD</th>
<th>FTD</th>
<th>MCI</th>
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<td>No</td>
<td>No</td>
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Blank = no data
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; 291:137)

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: Basics

- 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

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 Neurol. 2015 Jun 16;6:284) (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.

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