Management of Alzheimer’s Disease Dementia

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Disclosure

- I do not have a vested interest in or affiliation with any corporate organization offering financial support or grant money for this continuing education program, or any affiliation with an organization whose philosophy could potentially bias my presentation.
By the end of the presentation the pharmacist should be able to:

- Define dementia and describe the different types of dementia.
- Describe the pathophysiology of Alzheimer’s Disease (AD).
- Recognize and describe the different stages of AD associated with disease progression.
- Discuss non-pharmacological approaches in managing AD.
- Implement current standard of care for pharmacological treatment in patients with AD.
- Explain the pharmacists’ role in managing patients with AD.
By the end of the presentation the pharmacist technician should be able to:

- Define dementia and describe the different types of dementia.
- Describe the pathophysiology of AD.
- Identify the different stages of AD associated with disease progression.
- Recognize brand and generic names of medications used in the management of AD.
- Explain the pharmacist technicians’ role in interacting with patients with AD.
OVERVIEW

- Introduction
- Epidemiology
- Pathophysiology
- Etiology
- Risk Factors
- Clinical Presentation
- Diagnosis
- Treatment
RD is a 74 year old Hispanic male who was brought to a psychiatric facility after his wife called the police. RD lives with his wife, who helps take care of him. One Sunday morning, she was helping him get dressed for church when he all of a sudden began screaming “Who are you and where is my wife!!” while striking her repeatedly with his cane.

RD has no previous psychiatric hospital admissions and his medical conditions include hypertension, BPH, and glaucoma.

While interviewed by the police, RD seemed disoriented and his statements did not make sense.
DSM-5 Definition of Dementia

“Significant acquired cognitive impairment in one or more cognitive domains (e.g. learning and memory, language, executive function, complex attention, perceptual-motor function, social cognition) that represents a drastic decline from previous baseline and interferes with independence in daily activities.”

The most common types of dementia include:

- **Alzheimer’s disease dementia**
  - Gradually progressive dementia affecting cognition, behavior, and functional status
  - One of the leading causes of morbidity and mortality in the elderly
  - Accounts for 50-60% of dementia cases in the elderly

- **Vascular dementia**
  - Dementia caused by damage to the vasculature or impaired blood flow to the brain
  - Risk factors include stroke, hypertension, and diabetes
  - Accounts for 20% of all dementia cases
Frontotemporal dementia
- Degeneration of the frontal and/or temporal lobes
- Changes in personality, behavior and a progressive deterioration in language.
- Accounts for 10-20% of all dementia cases

Dementia with Lewy bodies (DLB)
- Cognitive dysfunction, visual hallucinations, and Parkinsonism symptoms
- Average age of onset is 75 years
- Accounts for less than 20% of all dementia cases
AD is the 6\textsuperscript{th} leading cause of death in the U.S.\textsuperscript{6}

As of 2017, 5 million individuals were living with AD in the U.S.\textsuperscript{6}

By 2050, AD is expected to affect 16 million individuals in the U.S. and > 130 million worldwide\textsuperscript{6}

In the U.S., the incidence of AD is higher in African Americans and lowest in Asian descent\textsuperscript{7}

Currently, AD and other dementias will cost the nation $259 billion, but is expected to rise as high as $1.1 trillion by 2050\textsuperscript{6}
PATHOPHYSIOLOGY

- Amyloid plaque accumulation\(^8\)
- Neurofibrillary tau tangles\(^8\)
- Depletion of acetylcholine\(^8\)
- [https://www.youtube.com/watch?v=NjgBnx1jVIU\(^9\)](https://www.youtube.com/watch?v=NjgBnx1jVIU)
Brain Atrophy in Advanced Alzheimer’s Disease

Normal

AD
ETIOLOGY/RISK FACTORS

- Genetic
  - Age
  - Family history
  - Rare genetic mutation in amyloid precursor protein (APP)\(^{10}\)
  - Apolipoprotein E (APOE) epsilon 4 (e4) allele\(^{2}\)

- Acquired\(^{10}\)
  - Elevated LDL levels
  - Cerebrovascular disease
  - Hypertension
  - Type 2 diabetes and obesity
  - Brain trauma
  - Medications
MEDICATIONS THAT AFFECT COGNITION

- Benzodiazepines
- Sedative hypnotics
- Anticholinergics
- Antihistamines
- Antipsychotics
- CNS depressants
- Skeletal muscle relaxants

General

- Patient may initially present with vague memory complaints, or their significant other may report that the patient is “forgetful”
- Cognitive decline is gradual over the course of illness
- Behavioral disturbances may be present in moderate stages
- Loss of ability to carry out daily functions is common in advanced stages

CLINICAL PRESENTATION

- Cognitive symptoms
  - Memory loss
    - Poor recall, losing items
  - Aphasia
    - Impaired speech and inability to comprehend
  - Apraxia
    - Difficulty performing tasks or movements when asked
  - Agnosia
    - Loss of ability to recognize or comprehend the meaning of objects even with intact senses
  - Disorientation
    - Impaired perception of time and inability to recognize familiar people
  - Impaired executive function
    - Difficulty concentrating and inability to multitask

CLINICAL PRESENTATION

- Noncognitive symptoms
  - Behavioral and psychological symptoms
    - Common during middle and late stages of AD
    - Agitation, aggression, wandering and psychosis (i.e., hallucinations and delusions)
  - Functional impairment
    - Inability to perform activities of daily living (ADLs)
      - Dressing, bathing, toileting, eating
  - Sleep disturbances
    - “Sundowning”

Nearly all patients with AD may develop BPSD with disease progression

Symptoms and frequency may vary, but include
- Hallucinations
- Delusions
- Agitation
- Depression
- Aggression
- Sleep disorders

Non-pharmacological approaches are recommended as golden standard

Some cases may require pharmacological management, which include:

- Antipsychotics
- Antidepressants
- Sedative and hypnotic agents
- Mood stabilizers
- Cholinesterase inhibitors
- Amantadine

More information on BPSD and management will be presented by another presenter following this presentation.
DIAGNOSIS
LABORATORY TESTS

- Rule out vitamin B12 and folate deficiency
- Thyroid function tests
- Complete blood cell count
- Electrolytes
- Liver function tests (LFTs)
- Urinalysis
- Imaging diagnostic tests
  - CT or MRI scan

MAJOR NEUROCOGNITIVE DISORDER DUE TO AD

- Evidence of significant cognitive decline from a previous level of performance in one or more of the following cognitive domains:
  - Learning and memory
  - Language
  - Executive function
  - Complex attention
  - Perceptual-motor

- Cognitive deficits interfere with independence in everyday activities. At a minimum, assistance should be required with complex ADLs (i.e. managing finances or managing medications)

- Cognitive deficits do not occur exclusively in the context of delirium

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The cognitive deficits are not caused by another psychiatric disorder (e.g., major depressive disorder, schizophrenia)

Insidious onset and gradual progression of impairment in at least 2 cognitive domains.

Either of the following:

- Evidence of a causative Alzheimer's disease genetic mutation from family history or genetic testing.
- All three of the following characteristics are present:
  1. Clear evidence of decline in memory and learning and at least one other cognitive domain (based on detailed history or serial neuropsychological testing).
  2. Steadily progressive, gradual decline in cognition, without extended plateaus.
  3. No evidence of mixed etiology (i.e., absence of other neurodegenerative or cerebrovascular disease, or another neurological, mental, or systemic disease or condition likely contributing to decline)

Disease severity can be measured with various mental status scales:

- **Mini-Mental State Examination (MMSE)**
  - 7 areas of cognitive function are assessed: orientation, registration, attention, calculation, recall, language and visual construction
  - Maximum score is 30, 24 or lower indicates cognitive impairment
  - Most commonly used, 5-10 minutes to administer.

- **Montreal Cognitive Assessment (MoCA)**
  - 10 minute, 30 point cognitive screening test used in patients with suspected mild cognitive impairment scoring (MMSE: 24-30)
  - Emphasis on frontal executive functioning and attention
  - 26 and below indicates cognitive impairment
Clinical Dementia Rating Scale

- Global rating estimated via interview of the patient and the caregiver
- Assess 6 different cognitive and behavioral domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies performance, and personal hygiene.
- Scores range from 0-3, $1\geq$ indicates cognitive impairment.
MMSE

- Composed of simple questions and problems in areas such as:
  - Time and place
  - Repeating words
  - Spelling the word “world” backwards
  - Drawing shapes
    - (i.e., two pentagons overlapping)

- Score Breakdown (may slightly vary depending upon source)
  - 25-30 Normal
  - 21-24 Mild cognitive impairment
  - 10-20 Moderate cognitive impairment
  - <10 Severe cognitive impairment

MINI MENTAL STATE EXAMINATION (MMSE)

Please name the:
Year?
Season?
Date?
Day of Week?
Month?

Orientation to time /5

Where are we?
State?
City?
Suburb?
Hospital?
Floor/Ward?

Orientation to place /5

“I am now going to test your memory”
Name 3 objects. Ask them to repeat all 3.
1 point for each object remembered. Repeat
until learnt all 3 so that recall can be tested.
Registration /3
# of trials

Serial 7s
“please count backwards from 100 in sevens”
93, 86, 79, 72, 65
Alternatively
Spell WORLD backwards
D L R O W

Attention and Calculation /5

“Please repeat the 3 objects I asked you to remember”
Recall /3

“Please name these objects”
Point to a wristwatch and a pencil
Naming /2

“Please repeat the following phrase”
“No ifs, ands or buts”
Repetition /1

“Please follow this command”
“Take this paper in your right hand, fold it in
half and place it in your lap”
Complex command /3

Please read and obey the following command
CLOSE YOUR EYES

“Please write a sentence”
Must have a noun, verb and make sense

“Please copy the following drawing”

1 point each for the last 3 commands /3

TOTAL /30

24-30-normal range
18-23-moderate cognitive
impairment
0-17-marked
cognitive impairment
Objective

Differentiate AD from mild cognitive impairment (MCI) using combination of MMSE and a Clock Drawing Test (CDT) vs. Alzheimer’s Disease Assessment Scale-cognitive subscale (ADAS-j cog)

Result

Combination of MMSE and CDT was more sensitive than MMSE alone
Sensitivity and specificity similar to ADAS-J cog

Conclusion

Combination of MMSE and CDT could be beneficial in differentiating AD from MCI

### Delirium vs. Dementia

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Delirium</th>
<th>Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Abrupt or suddenly (hours or days)</td>
<td>Gradual, over time (months or years)</td>
</tr>
<tr>
<td>Attention and orientation</td>
<td>Impaired</td>
<td>Usually not impaired, but may alter in later stages</td>
</tr>
<tr>
<td>Level of consciousness</td>
<td>Sometimes decreased</td>
<td>Normal</td>
</tr>
<tr>
<td>Speech and language</td>
<td>Disorganized, scattered</td>
<td>Difficulty formulating complete sentences</td>
</tr>
<tr>
<td>Memory for recent and past events</td>
<td>Varies (may or may not be able to recall)</td>
<td>Unable to recall recent events, memory for past events decreases as disease progresses</td>
</tr>
</tbody>
</table>

RD is a 74 year old Hispanic male who was brought to a psychiatric facility after his wife called the police. RD lives with his wife, who helps take care of him. One Sunday morning, she was helping him get dressed for church when he all of a sudden began screaming “Who are you and where is my wife!!” while striking her repeatedly with his cane.

RD has no previous psychiatric hospital admissions and his medical conditions include hypertension, BPH, and glaucoma.

While interviewed by the police, RD seemed disoriented and his statements did not make sense.
After RD was admitted, his vitals were taken, labs were drawn and a urinalysis was performed to further assess his condition.

BP: 145/92, HR: 96, R: 20, T: 99.9°F
### Patient Case 1: RD

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>140 mEq/L</td>
</tr>
<tr>
<td>BUN</td>
<td>15 mg/dL</td>
</tr>
<tr>
<td>Hgb</td>
<td>14.2 g/dL</td>
</tr>
<tr>
<td>K</td>
<td>4.5 mEq/L</td>
</tr>
<tr>
<td>Glucose</td>
<td>90 mg/dL</td>
</tr>
<tr>
<td>Hct</td>
<td>42.4%</td>
</tr>
<tr>
<td>Cl</td>
<td>104 mEq/L</td>
</tr>
<tr>
<td>TSH</td>
<td>2.5 mIU/L</td>
</tr>
<tr>
<td>AST</td>
<td>20 IU/L</td>
</tr>
<tr>
<td>CO₂</td>
<td>21 mEq/L</td>
</tr>
<tr>
<td>WBC</td>
<td><strong>14.5 x 10³/mm³</strong></td>
</tr>
<tr>
<td>ALT</td>
<td>23 IU/L</td>
</tr>
<tr>
<td>SrCr</td>
<td>1.1 mg/dL</td>
</tr>
<tr>
<td>ANC</td>
<td><strong>5.0 x 10³/mm³</strong></td>
</tr>
<tr>
<td>Platelets</td>
<td>246 x 10³/mm³</td>
</tr>
<tr>
<td>Color</td>
<td>Yellow</td>
</tr>
<tr>
<td>Specific gravity</td>
<td>1.020</td>
</tr>
<tr>
<td>Nitrates</td>
<td>(+)</td>
</tr>
<tr>
<td>Appearance</td>
<td>Cloudy</td>
</tr>
<tr>
<td>Glucose</td>
<td>(-)</td>
</tr>
<tr>
<td>Leukocyte esterase</td>
<td>LE +2</td>
</tr>
<tr>
<td>pH</td>
<td>8.9</td>
</tr>
<tr>
<td>Ketones</td>
<td>(-)</td>
</tr>
<tr>
<td>WBCs</td>
<td>(+3)</td>
</tr>
</tbody>
</table>
Which condition is RD most likely suffering from?

- A. Lewy Body Dementia
- B. Delirium
- C. Alzheimer’s Dementia
- D. Vascular Dementia
STAGING AD
STAGES OF AD

- Preclinical AD
- Mild cognitive impairment
- Moderate cognitive impairment
- Severe cognitive impairment

PRECLINICAL AD

- MMSE: 25\(\geq\)18
- Signs of memory loss can be reported by patient or caregiver\(^1^8\)
- Noticeable signs of memory impairment\(^2\)
- Mild language or executive dysfunction
- No functional impairment
- Estimated 6-15% of cases will progress to AD, however some may not\(^2\)
MILD COGNITIVE IMPAIRMENT

- MMSE: 24-21\(^\text{18}\)
- Difficulty remembering recent events\(^\text{2}\)
- Decline in ability to manage finances, prepare food, or carry out other household activities\(^\text{2}\)
- May get lost while driving\(^\text{2}\)
- Loss of interest in hobbies, unable to perform difficult tasks\(^\text{2}\)
- May deny memory problems\(^\text{18}\)
MODERATE COGNITIVE IMPAIRMENT

- MMSE: 20-10
- Requires assistance performing ADLs (i.e. bathing, dressing, grooming)
- Disorientation to time (i.e., date, year, and season)
- Recall of recent events is severely impaired
- Unable to recall details of past life and names of family members and friends
- Ability to function fluctuates daily
- Patient generally denies problems
- Loses ability to drive safely
- May become suspicious or tearful
- Agitation, paranoia, and delusions are common
SEVERE COGNITIVE IMPAIRMENT

- MMSE: <10
- Complete loss of remote memory
- Loses ability to speak, walk, and feed self (i.e., unable to perform ADLs)
- Incontinent of urine and feces
- Requires care 24 hours a day, 7 days a week
- Easily susceptible to conditions common in advanced dementia (i.e., pressure ulcers, constipation, pain, and infections)
- 71% of patients with advanced dementia admitted to nursing homes die within 6 months.

71% of patients with advanced dementia admitted to nursing homes die within 6 months.
SD is a 68 year old Caucasian male who presents to his primary care physician today with complaints of “forgetfulness.” SD lives with his wife, who is also present at the visit. She states that in the last 2 months he would sometimes forget to turn the stove off after cooking breakfast. She also reports 3 days ago while driving home from their son’s house, she had to redirect him because he seemed to have lost his sense of direction and could not remember the way back home. He states, “There is nothing wrong with me! I just got a little confused because it was getting dark and I was tired! I am getting older you know, these things sometimes happen!”

SD has a past medical history of hypertension and Type 2 diabetes
Patient Case 2: SD

- Labs were drawn and they were all normal
- The doctor decided to give SD the MMSE, where he scored a **22/30**
- He was diagnosed with Alzheimer’s disease
Which stage would you appropriately classify SD’s AD?

- A. Preclinical AD
- B. Severe cognitive impairment
- C. Mild cognitive impairment
- D. Moderate cognitive impairment
TREATMENT
GOALS OF THERAPY

- Improve or delay the loss of memory and cognition associated with disease progression
  - AD is progressive and irreversible, therefore treatment will not restore cognitive or functional ability

- Maintain independent function to perform ADLs

- Patient’s cognitive function should be reassessed periodically to determine if and when further intervention with medication is necessary

- Reduce the risk of mortality from infections and malnutrition/dehydration

TREATMENT

- Non-pharmacological

- Pharmacological
  - Acetylcholinesterase Inhibitors
    - Donepezil (Aricept®)
    - Rivastigmine (Exelon®)
    - Galantamine (Razadyne®)
  - NMDA Receptor Antagonist
    - Memantine (Namenda®)
  - Combination Agent
    - Memantine/donepezil (Namzaric®)

- Alternative Therapies
  - Gingko
  - Huperzine A
  - Vitamin E
NON-PHARMACOLOGICAL MANAGEMENT

- Engage in regular physical activity
- Mediterranean Diet
- Avoid alcohol
- Continue or begin activities that stimulate brain activity
- Stress management
- Family/caregiver education

ACETYLCHOLINESTERASE INHIBITORS

MOA: Inhibits acetylcholinesterase at the synaptic cleft, increasing the concentration of acetylcholine

<table>
<thead>
<tr>
<th>Name</th>
<th>Starting dose</th>
<th>Maintenance dose</th>
</tr>
</thead>
</table>
| Donepezil (Aricept®)        | 5 mg once daily                | 10 mg/day (increased after 4-6 weeks)²⁰  
Severe disease: 23 mg/day (max dose, may increase to 23 mg after 3 months of 10 mg/day)²⁰ |
| Rivastigmine (Exelon®)      | 1.5 mg PO BID                   | 6 mg PO BID, max dose (increased by 1.5 mg increments BID every 2 weeks)²¹       |
| Galantamine (Razadyne®, Razadyne®ER) | 4 mg BID, ER: 8 mg once daily | 12 mg BID, max dose (increased by 4 mg BID every 4 weeks)²³  
ER: 24 mg once daily, max dose (increased by 8 mg once daily every 4 weeks)²³ |
## ACETYLCHOLINESTERASE INHIBITORS

<table>
<thead>
<tr>
<th>Name</th>
<th>Formulation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil (Aricept®)</td>
<td>Oral tablet (5 mg, 10 mg, 23 mg)</td>
<td>May cause nausea/vomiting, diarrhea, insomnia, vivid dreams, bradycardia, QT-prolongation(^{20})</td>
</tr>
<tr>
<td></td>
<td>Orally disintegrating tablet (5 mg, 10 mg)</td>
<td>Per package insert, take at bedtime; however, it is usually taken in the morning due to side effects(^{20})</td>
</tr>
<tr>
<td>Rivastigmine (Exelon®)</td>
<td>Oral capsule (1.5 mg, 3 mg, 4.5 mg, 6 mg)</td>
<td>Patch: 4.6 mg/24 hours topically, titrate every 4 weeks to a max dose of 13.3 mg/24 hours (^{22})</td>
</tr>
<tr>
<td></td>
<td>Transdermal patch (4.6 mg/24 hours, 9.5 mg/24 hours, 13.3 mg/24 hours)</td>
<td>May cause significant GI upset (low incidence with patch), insomnia, bradycardia, skin irritation (patch)(^{21,22})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rotate sites of the patch to prevent skin irritation(^{22})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oral: take with meals to decrease GI side effects(^{21})</td>
</tr>
<tr>
<td>Galantamine (Razadyne®, Razadyne® ER)</td>
<td>Oral tablet (4 mg, 8 mg, 12 mg)</td>
<td>May cause GI upset, insomnia, bradycardia, weight loss(^{23})</td>
</tr>
<tr>
<td></td>
<td>Oral solution (4 mg/mL)</td>
<td>Take with meals to decrease GI upset(^{23})</td>
</tr>
<tr>
<td></td>
<td>Oral capsule, ER (8 mg, 16 mg, 24 mg)</td>
<td></td>
</tr>
</tbody>
</table>
Objective
Safety and efficacy of galantamine in AD at 3 months using flexible dose escalation.

Results
Galantamine produced significant improvement in cognitive function than placebo at 3 months (treatment difference = 1.9 points on ADAS-cog, p=0.002)
ADLs were improved, no significant changes in behavioral symptoms

Conclusion
Cognitive function and ADLs were improved with flexible dose escalation of galantamine

MEMANTINE (NAMENDA®, NAMENDA® XR)

- **Dosing**
  - IR tablet or oral solution: 5 mg QD initially
    - May titrate in 5 mg increments at intervals of at least 1 week to 10 mg/day. Max dose: **20 mg/day**
  - XR capsule: 7 mg QD initially
    - May titrate in 7 mg increments at intervals of at least 1 week if tolerated. Max dose: **28 mg/day**

- **Comments**
  - May cause headache, constipation, dizziness, confusion
  - Dosed twice daily if dose is > 5mg/day (IR)
  - XR capsules can be opened and sprinkled on applesauce

- **Formulations**
  - Oral tablet
    - 5 mg, 10 mg
  - XR capsule
    - 7 mg, 14 mg, 21 mg, 28 mg
  - Oral solution
    - 2 mg/mL

- **Indicated for** moderate to severe AD

- **N-methyl-D-aspartate (NMDA) receptor antagonist**

MEMANTINE/DONEPEZIL
(NAMZARIC®)

- Indicated for moderate-severe AD

- Formulations
  - Oral capsule, ER

- Dosing
  - If stabilized on donepezil but not currently taking memantine:
    - Begin 7 mg/10 mg QD for 1 week, may increase in 7 mg increments, no more than once weekly. Target dose: 28 mg/10mg

- Dosing cont’d
  - If stabilized on donepezil 10 mg and memantine 10 mg twice daily or 28 mg (ER)
    - Start fixed dose, ER combination 28 mg/10 mg

- Comments
  - May cause headache, constipation, dizziness, nausea/vomiting, anorexia
  - Given in the evening
  - Capsules may be opened and sprinkled on applesauce or other soft foods

DONEPEZIL VS. COMBINATION WITH MEMANTINE FOR AD

Objective
- Compare efficacy and safety of donepezil alone vs. combination of memantine and donepezil in moderate-severe AD

Results
- Greater improvements in cognitive functions, BPSD, and global functions with combination donepezil and memantine vs. donepezil alone

Conclusion
- Combination of donepezil and memantine may lead to greater improvement in cognitive functions, BPSD, and global functions than donepezil alone in moderate-severe AD

ALTERNATIVE THERAPIES
GINGKO BILOBA

- Plant extract (EGb761) with possible antioxidant and anti-inflammatory properties against AD

- Evidence
  - Dementia (Multiinfarct and Alzheimer’s Type): Grade A

- Dosing
  - 120 mg/day orally

- Side Effects
  - Headache, nausea, GI cramps

- Comments
  - Although proven safe, some studies show inconsistency with efficacy
  - Increased bleeding risk
    - (i.e. when used with other agents that increase risk of bleeding)

HUPERZINE A

- Potent selective and reversible acetylcholinesterase inhibitor
- Derived from the Chinese herb *Huperzia serrata*
- Approved in China by State Food and Drug Administration of China for AD in 1994
- Dosing
  - 50-200 mcg orally twice daily
- Side Effects
  - Same GI effects as AchE inhibitors (i.e. nausea, vomiting, diarrhea), bradycardia
- Comments
  - Available as dietary supplements
  - Not FDA approved in the U.S.
  - Should not be used in combination with AchE inhibitors

Objective
- Assess efficacy of Huperzine A in mild-moderate AD

Results
- No change in ADAS-Cog at 16 weeks with Huperzine A 200 mcg BID
- Huperzine A 400 mcg BID demonstrated a 2.27-point improvement in ADAS-cog at 11 weeks vs. 0.29-point decline with placebo

Conclusion
- Huperzine A 200 mcg BID did not show cognitive benefit in patients with mild-moderate AD
- A higher dose, 400 mcg BID may improve cognition

VITAMIN E

- Vitamin E (alpha-tocopherol) is believed to have neuroprotective properties in AD

- Evidence
  - Alzheimer’s Disease/Dementia: Grade C

- Dosing
  - 2,000 IU by mouth once daily

- Side Effects
  - Abdominal pain, nausea, diarrhea, flu-like symptoms (when taken at higher doses)

- Comments
  - Can be used as supplementation in mild-moderate AD

THERAPY CONSIDERATIONS
MILD-MODERATE DISEASE

- FDA Indicated
  - Donepezil (Aricept®)
  - Rivastigmine (Exelon®)
  - Galantamine (Razadyne®, Razadyne ER®)

- No difference in efficacy
  - Patient specific factors (i.e., side effect profile), prescriber’s preference and cost should be considered

- Initiation
  - Doses should be titrated over 4-6 weeks to maximum dosage and to assess efficacy and tolerability

- When to switch to a different AChE inhibitor
  - If GI adverse effects continue to worsen

### Patient Specific Factors

<table>
<thead>
<tr>
<th>Patient Specific Factors</th>
<th>Consider...</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intolerable GI side effects</td>
<td>Donepezil, rivastigmine patch</td>
<td>Donepezil, MAX dose: 10 mg once daily&lt;sup&gt;20&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rivastigmine patch, MAX: 13.3mg/24 hours applied once daily&lt;sup&gt;22&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficulty or unable to swallow pills</td>
<td>Donepezil ODT, rivastigmine patch, galantamine oral solution</td>
<td>Galantamine, MAX dose: 12 mg twice daily&lt;sup&gt;23&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost</td>
<td>Donepezil ($10)&lt;sup&gt;32&lt;/sup&gt;</td>
<td>Rivastigmine ($60.25)&lt;sup&gt;33&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Galantamine ($55.74)&lt;sup&gt;34&lt;/sup&gt;</td>
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MODERATE-SEVERE DISEASE

- **FDA Indicated**
  - **Donepezil (Aricept®)**
    - MAX: 23 mg orally once daily at 3 months\(^{20}\)
  - **Rivastigmine patch (Exelon®)**
    - Target: 9.5 mg/24 hours topically, MAX: 13.3 mg/24 hours topically\(^{22}\)
  - **Memantine (Namenda®, Namenda XR®)**
    - Target: 20 mg/day (IR), MAX: 28 mg/day (XR)\(^{25}\)
  - **Memantine/donepezil (Namzaric®)**
    - MAX: 28 mg/10 mg once daily\(^{26}\)

- **Memantine is only indicated for moderate to severe disease and can be used in combination with an AChE inhibitor**\(^{25}\)
The doctor decides to initiate therapy with donepezil 5 mg QD. One month later, the dose was increased to 10 mg QD.

3 months later, SD presents to his PC for a follow-up. His wife states that his memory continues to decline, and he forgets what day it is or the current month. She states that he sometimes calls her by his mom’s name, who has been deceased over 20 years. She also reports that he has trouble dressing himself and sometimes does not make it to the bathroom on time. He is also now unable to drive and has trouble swallowing.

SD is issued another MMSE, and the resulting score is now 16/30.
Which therapy recommendation would be MOST appropriate for SD?

- A. Increase Aricept® to 23 mg QD
- B. Switch from Aricept® to galantamine 2 mg BID
- C. Add Namenda® XR 7 mg BID
- D. Switch to Exelon® patch 4.6 mg/24 hours
If the doctor decides to start the Exelon® patch, how should he initiate therapy?

- A. Begin Exelon® 4.6 mg/24 hours topically and titrate once a week to max dose of 13.3 mg/24 hours
- B. Begin Exelon® 13.3 mg/24 hours topically
- C. Discontinue donepezil. Begin Exelon® 13.3 mg/24 hours topically
- D. Discontinue donepezil. Begin Exelon® 4.6 mg/24 hours topically and titrate every 4 weeks to max dose of 13.3 mg/24 hours
AR is a 78 year old African American female who is diagnosed with AD. She is currently on Aricept® 10 mg QD. Two months ago, her MMSE score was 21/30. Today she presents to her primary care physician for follow up, who issues her another MMSE. She scores a 14/30.

AR lives with her daughter, who helps her to perform most ADLs and manages her finances.

The doctor wants to begin therapy with Namzaric®.
Based on today’s visit, how would you appropriately classify AR’s AD?

- A. Moderate cognitive impairment
- B. Severe dementia
- C. Mild cognitive impairment
- D. Preclinical AD
How should Namzaric® be initiated in AR?

- A. Begin fixed dose combination of 28 mg/10 mg QD
- B. Begin 7 mg/10 mg QD and titrate by 7 mg increments twice weekly to target dose of 28 mg/10 mg
- C. Begin 7 mg/10 mg for 2 weeks, then titrate by 7 mg increments once weekly to target dose of 28 mg/10 mg QD
- D. Begin 7 mg/10 mg for 1 week, then titrate by 7 mg increments once weekly to target dose of 28 mg/10 mg QD
AR’s daughter now reports that she has difficulty swallowing. What would be the BEST recommendation?

- A. Discontinue Namzaric® and begin rivastigmine patch 4.6 mg/24 hours topically.
- B. Discontinue Namzaric®. Begin donepezil ODT 10 mg QD in combination with memantine oral solution 5 mg QD.
- C. Inform the daughter that the Namzaric® capsules can be opened and sprinkled onto soft foods, such as applesauce.
- D. Discontinue Namzaric® and begin Razadyne® oral solution 4 mg BID.
ADVANCED DEMENTIA
ADVANCED DEMENTIA

- One of the leading causes of death in the elderly in the United States

- Clinical features
  - Inability to recognize family members, minimal verbal communication, loss of ambulatory function, urinary and fecal incontinence

- Difficulty swallowing and infections are the most common complications

- Palliative and hospice care should be offered if available

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Clinical Complications
- Eating difficulties
  - Patients may refuse to eat or be unable to swallow
  - Hand feeding or tube feedings are options, to ensure adequate caloric intake
  - Risks of tube feedings include insertion complications and blockages

Infections
- Approximately half of these patients are diagnosed with pneumonia in the last 2 weeks of life
- Most common cause of hospitalization
- Urinary tract infections are also common
- If comfort is the main goal, symptoms should be managed only, avoiding the use of antimicrobials
Palliative and Hospice Care

- Goal of care is comfort
- Pain is difficult to assess
- Studies prove that patients enrolled in hospice have a lower chance of dying in the hospital
- Increased chances of being treated for pain and dyspnea
- Agitation is best managed with non pharmacological approaches

Medication Use

- Discontinue medications with no known benefits
- Inappropriately prescribed medications in nursing home residents with advanced dementia included:
  - AChE inhibitors (36%)
  - Memantine (25%)
  - Statins (22%)
- AChE inhibitors and memantine can be tapered over a 2-4 week period

SUMMARY OF GUIDELINES

- Mild-moderate Alzheimer’s Disease
  - Initiate therapy with an AChE inhibitor\(^{33}\)

- Moderate-severe Alzheimer’s Disease
  - Memantine can be initiated in combination with an AChE inhibitor\(^{33}\)

- Therapy should be evaluated within 3-6 months\(^{19}\)
  - Improvement or worsening since baseline should be noted

- If the patient continues to decline, determine if there is any benefit to continuing treatment\(^{19}\)

- If treatment is discontinued, AChE inhibitors and memantine should be tapered\(^{19}\)
WHAT’S IN THE PIPELINES
Study Type
- Phase 2, randomized clinical trial

Purpose
- Efficacy of riluzole, a glutamate modulator agent in patients with mild AD
- Evaluation of changes in cognitive function and two vivo biomarkers (e.g. Magnetic Resonance Spectroscopy (MRS) and FDG-PET)

Official title
- Glutamatergic Dysfunction in Cognitive Aging: Rizuzole in Mild Alzheimer’s Disease

Estimated Completion Date
- November 2019
PINS STIMULATOR SYSTEM FOR AD

- **Study Type**
  - Interventional, open label trial

- **Purpose**
  - Determine long-term effectiveness and safety of a bilateral deep brain stimulation (DBS) for patients with cognitive, behavioral, and functional disability in AD

- **Official Title**
  - The Safety and Efficacy of Long-term Treatment of PINS Stimulator System for patients with Alzheimer’s Disease

- **Estimated Completion**
  - December 2018

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AD is a progressive neurodegenerative disease, causing morbidity and mortality in the elderly\textsuperscript{2}

Genetics and other risk factors are major determinations of disease development\textsuperscript{7}

Stages of AD can be determined by degree of cognitive impairment\textsuperscript{18}

AChE inhibitors and memantine are the mainstay of therapy\textsuperscript{19}

Alternative therapies have shown limited efficacy\textsuperscript{19}

Comfort should be the main goal of care in advanced dementia\textsuperscript{35}

Future developments in the treatment of AD continue to flourish
QUESTIONS??

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