Disclosures

Clarifying Dementia Disorientation is accredited by ACPE for pharmacists, ACPE 0154-0000-15-045-L01-P, and technicians, ACPE 0154-0000-15-045-L01-T, for 1 contact hour.

Blair Sarbacker has not disclosed any financial or conflicts of interest in relation to this program.

Learning Objectives

At the end of this program, pharmacists and technicians should be able to:

- Differentiate between the most common types of dementia
- In a case scenario, recommend the appropriate medications for dementia, based on the type and stage of dementia
- When reviewing a medication list, identify drugs that can potentiate dementia or induce delirium in patients with dementia

What is Dementia?

- An acquired syndrome of decline in memory and at least 1 other cognitive function sufficient to affect daily life in an alert patient
  - Language, executive, etc
  - Progressive & disabling
  - Not a normal aspect of aging

AGS. A Guide to Dementia Diagnosis and Treatment
Normal Aging

- Some decline in processing and recall of new information
  - Slower, harder
- Reminders work
  - Visual tips, notes
- Word finding difficulty
- Difficulty with divided attention
- No consistent, progressive deviations on testing of memory
- Absence of significant effects on ADLs or IADLs due to cognition

Activities of Daily Living (ADLs)

- Dressing
- Eating
- Ambulating
- Toileting
- Hygiene – bathing

Instrumental Activities of Daily Living (IADLs)

- Shopping
- Housework – cleaning, laundry
- Accounting
- Food Preparation
- Transportation
- Medication management

Frequencies of Dementia Causes

- Alzheimer’s
- Other Progressive Disorders*
- Completely Reversible Causes**

Delirium vs. Dementia

Delirium and dementia can occur together. The distinguishing signs of delirium are:
- Disturbance in attention and awareness
  - Acute onset (hours to days)
  - Fluctuates in severity
- Additional disturbance in cognition
  - Has an attributable cause

Mild Cognitive Impairment

- Memory problem without deficits in other domains
- Objective impairment with validated memory screening tools
- No functional impairment
- Absence of delirium
- 12% per year progress to Alzheimer’s disease
- SLUMS 21-26 (w/ high school education)
- MMSE 26-30
- FAST 3

**AGS. A Guide to Dementia Diagnosis and Treatment
Types of Dementia
- Alzheimer Disease
- Vascular Dementia
- Lewy Body Dementia
- Frontotemporal Dementia
- Normal Pressure Hydrocephalus

Patient Case Scenario
LP is a 67 year old female who presents with increased confusion. She was recently discharged from the hospital after having a stroke. Her SLUMS shows dementia.

Progression of Dementia

<table>
<thead>
<tr>
<th>Level</th>
<th>MMSE</th>
<th>SLUMS</th>
<th>FAST</th>
<th>Cognitive Symptoms</th>
<th>Motor Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>21–25</td>
<td>1–20</td>
<td>4–6</td>
<td>Disoriented to date, Naming difficulties, Mild difficulty copying figures, Problems managing finances</td>
<td>Rare early, apraxia later</td>
</tr>
<tr>
<td>Moderate</td>
<td>11–20</td>
<td>1–20</td>
<td>5–6</td>
<td>Disoriented to date, Place, Comprehension difficulties, Impaired calculating skills, Impaired new learning</td>
<td>Rare early, apraxia later</td>
</tr>
<tr>
<td>Severe</td>
<td>0–10</td>
<td>1–20</td>
<td>7</td>
<td>Remote memory gone, Nearly unintelligible verbal output, Unable to copy or write</td>
<td>No longer grooming or dressing</td>
</tr>
</tbody>
</table>

Alzheimer Disease (AD)

- Onset: Gradual
- Cognitive Symptoms: Primarily memory with difficulty learning new information
- Motor Symptoms: Rare early, apraxia later
- Progression: Gradual, over 8-10 yr on average
- Imaging: Possible global atrophy, small hippocampal volumes

Alzheimer Disease – DSM-5
- All three of the following are present:
  1. Clear evidence of decline in memory and learning and at least one other cognitive domain
  - Complex attention, executive function, perceptual-motor, social cognition
  2. Steadily progressive, gradual decline in cognition, without extended plateaus
  3. No evidence of mixed etiology

AGS: A Guide to Dementia Diagnosis and Treatment.
APA: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.
Alzheimer's Disease

- Early onset: 40 – 64
- Late onset: 65 and older


Vascular Dementia

- Onset: May be sudden or stepwise
- Symptoms: Dependant upon anatomy of ischemia
- Progression: Stepwise with further ischemia
- Imaging: Cortical or subcortical changes on MRI


Lewy Body Dementia

- Onset: Gradual
- Cognitive Symptoms: Memory, visuospatial, hallucinations, fluctuating symptoms
- Motor Symptoms: Parkinsonism
- Progression: Gradual, but usually faster than AD
- Imaging: Possible global atrophy


Frontotemporal Dementia

- Onset: Gradual, usually age <60
- Cognitive Symptoms: Executive: disinhibition, apathy, behavior changes
- Motor Symptoms: None; may be associated with ALS in rare cases
- Progression: Gradual but faster than AD
- Imaging: Atrophy in frontal and temporal lobes


Normal Pressure Hydrocephalus (NPH)

- Onset: Sudden
- Cognitive Symptoms: Confusion, delayed cognition
- Motor Symptoms: Unsteady gait, incontinence
- Progression: Days; can recur if no stent placed
- Imaging: Enlarged ventricles


TREATMENT

Goal: To enhance quality of life and maximize functional performance by improving cognition, mood, and behavior
### Treatment

#### Non-Pharmacologic
- Consider vision & hearing impairment
- Physical therapy
- Mental activity
- Structured routine
- Environmental modification
- Safety precautions

#### Pharmacologic
- Cholinesterase inhibitors (ChIs)
- NMDA antagonist

### Treatment Controversy
- How to determine effectiveness
- Objective assessment
- Lacking clinical trials regarding:
  - Dose-response relationship
  - Maximum tolerated dose
  - Length of benefit

### Patient Case Scenario
- TR is a 77 yr old male who lives at home. His son (caregiver) states that he has recently been getting lost while driving. He has had 2 car accidents in the last year. The patient reports that he has been misplacing things more frequently than usual, such as his glasses and the remote.
- TR’s physician diagnoses him with mild dementia, likely Alzheimer type and calls you for a treatment recommendation
- PMH: HTN; BPH; HLP
- Current Medications: Tamsulosin; lisinopril; simvastatin
- SH:
  - Widowed
  - Retired mechanic; 10th grade education
  - Quit smoking 10 years ago (40 year pack history)

### Treatment Controversy
- Natural disease progression studies
- Average ADAS-cog increase
  - 4 points over 6 months
  - 7 points over 1 year
- General consensus
  - 4 point change = clinically significant
  - ADAS-cog not used in clinical practice b/c lengthy
  - MMSE:
    - Untreated pt – average decline 2-4 points per year

### Treatment Controversy
- Studies have shown modest clinical benefits for short- and long-term treatment with cholinesterase inhibitors (ChIs)
- Treatment for 6 months with ChIs improved cognitive function on average 2.7 points on the 70-point ADAS-cog Subscale, and showed small improvement on measures of ADLs and behavior

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When to Initiate in AD

When to Initiate in AD

Mild to Moderate

Moderate to Severe

Chl

Chl

NMDA Antagonist

AGS. A Guide to Dementia Diagnosis and Treatment.

Donepezil (Aricept®)

- 23 mg dose:
  - Randomized, double-blind, controlled study
  - Moderate to severe AD (MMSE 0-20)
  - Severe Impairment Battery to assess cognitive function
  - Designed for severely demented who are unable to take standard Neuropsych tests
  - Most items scaled on a 3 point scale (2 = correct, 1 = partially correct, 0 = incorrect)
  - Score range: 0 to 100 points
  - Statistically significant with a 2.2 point difference
  - Clinical significance?

Cholinesterase Inhibitors

- Donepezil (Aricept®)
- Rivastigmine (Exelon®)
- Galantamine (Razadyne®)
- Acetylcholinesterase inhibitors (AChIs)
- Cognitive enhancers

Donepezil (Aricept®)

- Slow acetylcholine breakdown
- No evidence of difference in efficacy among drugs

Dosing

- Mild to moderate
  - Initial dose: 5 mg/day
  - Can titrate to 10 mg/day after 4-6 weeks

Donepezil (Aricept®)

- Moderate to severe
  - Initial dose: 5 mg/day
  - Can titrate to 10 mg/day after 4-6 weeks
  - Can titrate to 23 mg/day after 12 weeks

Administration

- before bedtime
- 23mg – do not split, crush or chew

Donepezil (Aricept®)

- Common adverse effects
  - Nausea, diarrhea, vomiting, muscle cramps, fatigue, anorexia
  - Less common: increase dreaming, disturbed sleep
  - Can dose in AM
  - Bradycardia or syncopal episodes
  - Can switch to alternative ChI
  - Clinically significant weight loss reported in 8.4% and 4.9% of patients receiving 23 mg and 10 mg of donepezil, respectively

Donepezil (Aricept®)

- Press to severe
  - Initial dose: 5 mg/day
  - Can titrate to 10 mg/day after 4-6 weeks
  - Can titrate to 23 mg/day after 12 weeks

Donepezil (Aricept®)

- before bedtime
- 23mg – do not split, crush or chew

Micromedex® Healthcare Series [Internet database].

 Micromedex® Healthcare Series [Internet database].
Rivastigmine (Exelon®)

- **Indications**
  - Mild to moderate dementia associated with Alzheimer or Parkinson’s disease

- **Dosage forms:**
  - Capsule (generic), solution, patch

- **Evidence in Alzheimer’s:**
  - Mean improvement of 4.9 on ADAS-cog

- **Evidence in Parkinson’s:**
  - Mild to moderate dementia associated with Parkinson’s disease
  - Moderate improvement in dementia (Improvement of 4 on ADAS-cog)
  - Higher rates of nausea, vomiting, and tremor

- **Transdermal**
  - Initial: 1.5 mg PO BID
  - Can increase by 3 mg/day every 2 weeks
  - Max: 6 mg PO BID

- **Oral**
  - Initial: 4.6 mg/24 hour patch
  - Can titrate to 9.5 mg/24 hour patch after 4 weeks
  - If nausea, diarrhea, vomiting, or loss of appetite occur and treatment is interrupted:
    - If < 3 days reinitiate at same or lower dose
    - If > 3 days, reinitiate with lowest daily dose and titrate
  - Max dose 13.3 mg/24 hour – higher doses confer no additional benefit

- **Converting from oral to transdermal**
  - Apply first patch on day following last oral dose
  - Can increase after 4 weeks

- **Renal, hepatic – 4.6 mg/24 h max dose**
- **Body weight <50 kg – titrate carefully**
  - If toxicities occur, use 4.6 mg/24 h as maintenance dose

Galantamine (Razadyne®, Razadyne ER®)

- **Indications**
  - Mild to moderate Alzheimer’s dementia

- **Evidence**
  - Numerous large, prospective, randomized, double-blind, placebo-controlled studies
  - 3 – 6 months duration
  - Mild to moderate Alzheimer disease
  - Efficacy when dosed at 24 mg/day
  - Mean improvement of 3 to 4 point ADAS-cog

- **Availability:**
  - Tablet – IR & ER
  - Solution

- **If therapy interrupted for ≥ 3 days, must restart at lowest dose and increase to current dose**

- **Common adverse effects**
  - Nausea, vomiting, diarrhea, anorexia, weight loss
Galantamine (Razadyne®, Razadyne ER®)

Immediate Release
• Administer at breakfast and dinner
• Initial: 4 mg PO BID
• Titrate to 8 mg PO BID after 4 weeks
• Titrate to 12 mg PO BID after 4 weeks

Extended Release
• Administer in the morning with food
• Initial: 8 mg/day
• Titrate to 16 mg/day after 4 weeks
• Titrate to 24 mg/day after 4 weeks

NMDA Antagonists – memantine (Namenda)

• Indications
  • Moderate to severe dementia of the Alzheimer disease

• Availability
  • Tablets & solution
  • Extended release

• IR Dosing
  • Initial: 5 mg PO Q Day x 1 week,
  • Increase to 5 mg PO BID x 1 week,
  • Increase to 10 mg PO Q Day x 1 week,
  • Increase to 10 mg PO BID

• Dose adjust in severe renal disease

Memantine IR (Namenda)

• Evidence – Alzheimer Disease
  • Cochrane review – significant reduction in functional decline, cognitive deterioration, and agitation
  • Many other studies with inconsistent results

• Mild to moderate vascular dementia
  • 2 multicenter, double-blind, randomized, controlled trials
  • 28-weeks comparing memantine 10 mg BID vs. placebo
  • ADAS cog improvement of 1.79 and 2 – not statistically significant (CI crossed 1)

Memantine ER (Namenda XR®)

• Dosing:
  • Initial: 7 mg daily
  • Increase weekly in 7 mg increments
  • Maintenance dose: 28 mg daily

• Evidence – Alzheimer Disease
  • SIB improvement of 2.6 units

• No evidence in vascular dementia

Patient Case Scenario Continued

• After being stabilized on rivastigmine 6 mg po bid for 1 year, TR is administered another FAST to monitor for further changes in cognition.

• He receives a FAST score of 6 → moderate to severe dementia

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*Note: Images and tables within the document have been omitted for brevity. For full content, please refer to the original source.*
Memantine (Namenda®)

- Use in addition to ChI if ChI is considered to be effective
- Use as monotherapy if pt cannot tolerate ChI, ChI is ineffective, or ChI is contraindicated
- Common adverse effects
  - Constipation, confusion, dizziness, headache, sedation, agitation, falls

Other Potential Treatment Options

- Estrogen replacement
  - Conflicting evidence
- NSAIDs
  - Inflammatory process seen upon autopsy
  - No supportive evidence
- Vitamin E
  - Increased mortality at high doses
- Ginkgo Biloba
- Axona

Overview of Recommendations

- Alzheimer’s Disease:
  - Mild to moderate – ChI
  - Moderate to severe – ChI + memantine
- Vascular Dementia:
  - Evidence to support the use of ChIs is weak – not recommended
  - Memantine
- Parkinson’s Disease Dementia:
  - ChI
  - Frontotemporal Dementia:
    - No role for ChIs – may worsen agitation
  - Lewy Body Dementia:
    - No evidence
  - NPH:
    - Lumbar puncture (50 mL)

Patient Case Scenario

- RR is a 76 year old male who presents to the pharmacy for medication therapy management.
  - PMH:
    - Dementia
    - HTN
    - BPH
    - GERD
  - Medications:
    - Donepezil
    - Tamsulosin
    - Finasteride
    - Valsartan
    - Ranitidine

Drugs to Avoid in Dementia

Patient Case Scenario

- GW is an 86 year old female who presents to the pharmacy for medication therapy management.

- PMH:
  - Dementia
  - HTN
  - Depression
  - DM

- Medications:
  - Rivastigmine
  - Enalapril
  - Amitriptyline
  - Lantus

References

LP is a 67 year old female who presents with increased confusion. She was recently discharged from the hospital after having a stroke. Her SLUMS shows dementia. Which type of dementia is the patient most-likely presenting with?

A. Alzheimer Disease
B. Vascular Dementia
C. Lewy Body Dementia
D. Frontotemporal Dementia

TR is a 77 yr old male who lives at home. His son (caregiver) states that he has recently been getting lost while driving. He has had 2 car accidents in the last year. The patient reports that he has been misplacing things more frequently than usual, such as his glasses and the remote.

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PMH: HTN; BPH; HLP
Current Medications:
- Tamsulosin
- Lisinopril
- Simvastatin
SH:
- Widowed
- Retired mechanic; 10th grade education
- Quit smoking 10 years ago (40 year pack history)

The BEST treatment for TR’s dementia is:

A. Cholinesterase inhibitor
B. NMDA antagonist

What modifications would you like to make to his current medication regimen?

A. Increase rivastigmine to 12 mg po BID
B. Add galantamine ER 8 mg PO QAM with food
C. Add memantine 5 mg po Q Day
D. No changes

RR is a 76 year old male who presents to the pharmacy for medication therapy management.

PMH:
- Dementia
- HTN
- BPH
- GERD

Medications:
- Donepezil
- Tamsulosin
- Finasteride
- Valsartan
- Ranitidine
Which of his medications can worsen his cognitive impairment?

A. Tamsulosin
B. Finasteride
C. Valsartan
D. Ranitidine

Patient Case Scenario

GW is an 86 year old female who presents to the pharmacy for medication therapy management.

- PMH:
  - Dementia
  - HTN
  - Depression
  - DM

- Medications:
  - Rivastigmine
  - Enalapril
  - Amitriptyline
  - Lantus

Which of her medications can cause delirium?

A. Rivastigmine
B. Enalapril
C. Amitriptyline
D. Lantus