DEMENTIA: TYPES, STAGES AND SLEEP DISTURBANCES

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Disclosures

- Dr. Crouse has nothing to disclose
Objectives

1. Compare and contrast different types of dementia
2. Differentiate between stages of dementia and role of pharmacotherapy in each stage
3. List pros and cons of medications to treat sleep disturbances in dementia
Which type of dementia is characterized by visual hallucinations especially of small animals and objects?

A. Alzheimer’s  
B. Vascular  
C. Lewy-body  
D. Fronto-temporal
Memantine is FDA indicated for which stage of Alzheimer’s disease?
A. Mild cognitive impairment
B. Mild/moderate
C. Moderate/severe
D. Only in combination with donepezil for mild/moderate
Rapid-eye movement (REM) sleep behavior disorder is associated with which type of dementia?

A. Alzheimer’s
B. Vascular
C. Lewy-body
D. Fronto-temporal
Which of the following is a risk associated with use of zolpidem in elderly patients?

A. Falls with injury
B. Decreased appetite
C. Cognitive Impairment
D. Anticholinergic effects
TYPES OF DEMENTIA
Change in Terminology

<table>
<thead>
<tr>
<th>DSM-IV</th>
<th>DSM-5</th>
</tr>
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<tbody>
<tr>
<td>• Dementia</td>
<td>• Neurocognitive Disorder</td>
</tr>
</tbody>
</table>

DSM = Diagnostic and Statistical Manual of Mental Disorders
DSM-5 Am Psychiatric Assoc 2013
Evidence of a significant decline in cognitive function from previous level in ≥ 1 cognitive domain

- Complex attention, executive function, learning and memory, language, perceptual-motor or social cognition
- Based on: individual concern, a family member, or the clinician
- Substantial impairment in cognitive performance
- Interferes with every day activities [instrumental activities of daily living (iADLs)]
- Not caused by delirium

DSM-5, Am Psychiatric Assoc 2013
Types of Dementia

Alzheimer-related, HIV infection, Traumatic Brain Injury (TBI), Huntington’s, Prion Disease

Alz + Vascular (Vasc)
Alz + Lewy-body (LB)
Alz + LB + Vasc

Vascular
Lewy-Body
Alzheimer’s
Other
Mixed
Parkinson’s
Fronto-temporal
# Prevalence of Dementia

<table>
<thead>
<tr>
<th>Type of Dementia</th>
<th>Description</th>
</tr>
</thead>
</table>
| Alzheimer’s                      | 60 – 80% of cases 
~ 30-40% solely Alzheimer’s; the remaining mixed pathology       |
| Vascular                         | Seen in 40% of cases 
~ 10% solely vascular changes                                             |
| Fronto-temporal dementia         | 10% of cases 
2nd most common type in persons < 65 years old                          |
| Lewy-Body dementia               | 4-7% of new diagnosis                                                        |
| Parkinson’s dementia             | 6-8%                                                                         |

Alzheimer’s Dementia

- Onset: later in life
- Symptoms:
  - Early: difficulty remembering recent events (conversations, most recent meal)
  - Later: confusion, poor judgment, reduced communication, behavioral changes
- Co-morbid symptoms: depression, anxiety, apathy

Age and Alzheimer’s Disease

% of Americans with Alzheimer's Disease (by age)

- 85+ years: 37%
- 75-84 years: 43%
- 65-74 years: 16%
- <65 years: 4%

Alzheimer’s Dementia – Decline in functioning over time
Vascular Dementia

- Onset: older age
- Risk factors: Cerebrovascular and cardiovascular diseases
  - Can result from: infarction, hemorrhage, white matter lesions, embolism, small vessel or large artery disease
- Often part of a mixed pathology in patient’s with Alzheimer’s
- Symptoms: impaired decision making ability, impaired executive functioning (planning or organizing), speed of information processing
  - Vascular Behavioral and Cognitive Disorders Society (Vas-Cog) also suggests accompanied by urinary symptoms, gait disturbance or personality changes
- Two types:
  - Post-stroke: immediate consequence of cognitive impairment
  - Without recent stroke: a result of vascular brain injury (usually detected on neuroimaging or neuropathology)

Vascular Dementia: Decline in functioning over time

- TIA
- CVA
- Hypoxic Injury from pulmonary embolism

Time
Lewy-Body Dementia or Dementia with Lewy-Bodies

- Risk factors: Older age; Males gender
- Symptoms: Well-formed visual hallucinations, slowed gait or gait imbalance, Parkinsonian movements, visual-spatial impairment, REM-Sleep behavior disorder
- Other features: falls, antipsychotic sensitivity, autonomic dysfunction (postural instability, incontinence)
- More psychiatric disturbances than Alzheimer’s and may have a higher rate of falls and respiratory infections

- Diagnostic triad/core criteria
  - Parkinsonism
  - Hallucinations (visual)
  - Alterations in attention and alertness
  - REM behavior disorder

Most recent consensus guidelines (2017) have put increased focus on REM sleep behavior disorder

Alzheimers Dement 2018;14(3):367-429; Postuma R. Mov Disord 2012;27(1):6-7.; Capouch SD Neurol Ther 2018
Parkinson’s Dementia

- Risk factors for cognitive impairment in patients with Parkinson’s disease
  - Atypical motor features
  - Greater motor impairment
  - Hallucinations earlier in course
  - Long duration of illness
  - Male
  - Age
Lewy-Body Dementia (DLB) vs. Parkinson’s Dementia (PDD)

**DLB**
- Dementia
- Parkinsonism

**PDD**
- Parkinsonism
- Dementia

Onset of Parkinson’s → Dementia
- DLB = 1 year
- PDD = 10 year

Capouch SD. Neurol Ther 2018
Fronto-Temporal Dementia

- Includes: Primary progressive aphasia, “Pick’s Disease”, corticobasal degeneration, progressive supranuclear palsy
- Age of onset: often earlier than Alzheimer’s.
  - Can occur after 65 years old
  - ~60% of patients with FTD are 45-60 years old
- Early symptoms: Change in personality or behavior; initially memory may not be affected

MEDICAL CAUSES OF COGNITIVE IMPAIRMENT
Normal Pressure Hydrocephalus

Wobbly
Wacky
Wet

< 5% of dementia cases
Risk factors: h/o brain hemorrhage or meningitis
Treatment: Surgical -> shunt to drain excess fluid

Classic Magnetic wide-based gait
https://www.youtube.com/watch?v=hziyFfJTrQo
https://www.youtube.com/watch?v=PTQx6wTVS80

Creutzfeld-Jakob disease (a.k.a “Mad Cow disease”) is extremely rare. The age of onset can vary across the spectrum, with the onset being rapid. Symptoms include rapid progression of impairments in memory, coordination, and behavioral changes, and the disease is fatal and irreversible. The source of information is [Alzheimer's Association](https://www.alz.org/media/HomeOffice/Facts%20and%20Figures/facts-and-figures.pdf) (2018).
Lyme Disease

- Early Symptoms → 3-30 days after bite
  - Fever, chills, headache, fatigue, muscle and joint aches, erythema migrans (EM) rash (70-80% of cases)

- Late Symptoms → days to months to years after bite
  - Headaches, neck stiffness
  - Additional EM rashes
  - Arthritis
  - Facial Palsy
  - Heart palpitations, irregular heart beat
  - Nerve pain
  - Short-term memory problems

- Treatment:
  - Acute lyme: PO doxycycline*, amoxicillin, or cefuroxime x14-21 days
    - *doxycycline 10-21 days
  - Neurologic disease: IV ceftriaxone, cefotaxime or PCN G x10-28 days

https://www.cdc.gov/lyme/resources/brochure/lymediseasebrochure.pdf
Other Reversible Causes

- Nutritional: Vitamin B12 deficiency, Folate Deficiency
- Endocrine: Hypo/hyperthyroidism; hypoparathyroidism
- Systemic lupus erythematosus
- Infections: Neurosyphilis, chronic meningitis, AIDs
- Drug side effects: anticholinergics, ?benzodiazepines?
- Psychiatric: depression, cognitive impairment in schizophrenia
- Other: Chronic obstructive pulmonary disease (COPD); Sleep apnea

Which type of dementia is characterized by visual hallucinations especially of small animals and objects?

A. Alzheimer’s  
B. Vascular  
C. Lewy-body  
D. Fronto-temporal
A 72 year old male with a history of diabetes, coronary artery disease, an myocardial infarction (MI) at age 49, and generalized anxiety was admitted for a change in behavior over the last 12 hours and was found to have a stroke on MRI. Prior to admission, he did not have any cognitive impairment. However now 2 months after the event at rehab, every day keeps asking “Why am I here?” “No one has told me why I am here”. Which type of dementia is at the top of your differential?

A. Alzheimer’s  
B. Vascular  
C. Lewy-body  
D. Fronto-temporal
An elderly patient has begun repeating the same question over and over again. She complains that someone is breaking into her house and stealing her keys and wallet. She reports there is less money in her bank account because someone is stealing her money. This presentation is consistent with which type of dementia?

A. Alzheimer’s
B. Vascular
C. Lewy-body
D. Fronto-temporal
SEVERITY OF DEMENTIA
Screening Tools

Cognitive Screening Tools

- Mini-Mental State Exam (MMSE) by Folstein et al.
- Blessed Orientation, Memory, Concentration (BOMC)
- St. Louis University Mental Status (SLUMS)
- Montreal Cognitive Assessment (MoCA)

Psychologist Administered

- Neuropsychological Testing
MMSE Examination

11 items scored; 30 points maximum

- 5 orientation questions (year, season, date, day of week, month)
- 5 location orientation questions (state, county, city; building (e.g. hospital), floor)
- 3-item recall (immediate and delayed)
- Concentration activity: Serial sevens or spell world backwards
- Naming activity – point to and have them name 2 separate objects
- Phrase repetition – Must say all 3 “s”s – No ifs, ands or buts
- 3-step command – Assesses executive function
- Have them read and sentence and do what it says (“Close your eyes”)
- Have them write a sentence
- Copy/draw intersecting pentagons – This assess visual-spatial

University of Massachusetts Lowell: https://www.uml.edu/docs/Mini%20Mental%20State%20Exam_tcm18-169319.pdf
Which was adapted from Rovner and Folstein Hosp Pract (1987) and Folstein et al. J Psychiatr Res (1975)
# MMSE Scoring – by Education?

<table>
<thead>
<tr>
<th>Scoring</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Cutoff</td>
<td>&lt; 24 Abnormal</td>
</tr>
<tr>
<td></td>
<td>&lt; 21 Increased possibility of dementia</td>
</tr>
<tr>
<td></td>
<td>&gt; 25 Reduced odds of dementia</td>
</tr>
<tr>
<td>Range</td>
<td>&lt; 21 Increased possibility of dementia</td>
</tr>
<tr>
<td>Education</td>
<td>&gt; 25 Reduced odds of dementia</td>
</tr>
<tr>
<td></td>
<td>21 Abnormal for 8th grade education</td>
</tr>
<tr>
<td></td>
<td>&lt; 23 Abnormal for high school education</td>
</tr>
<tr>
<td></td>
<td>&lt; 24 Abnormal for college education</td>
</tr>
<tr>
<td>Severity</td>
<td>24-30 No impairment</td>
</tr>
<tr>
<td></td>
<td>18-23 Mild impairment</td>
</tr>
<tr>
<td></td>
<td>≤ 17 Severe impairment</td>
</tr>
</tbody>
</table>

Maximum Score: 30

**Note some scoring references suggest:**
- Mild 19-23
- Moderate 10-18
- Severe < 10

University of Massachusetts Lowell: [https://www.uml.edu/docs/Mini%20Mental%20State%20Exam_tcm18-169319.pdf](https://www.uml.edu/docs/Mini%20Mental%20State%20Exam_tcm18-169319.pdf)

University of Iowa: [www.medicine.uiowa.edu/igec/tools/cognitive/MMSE.pdf](http://www.medicine.uiowa.edu/igec/tools/cognitive/MMSE.pdf)

http://www.dementiatoday.com/wp-content/uploads/2012/06/Mini
SLUMS Examination

11 questions total; 30 points maximum
• 3 orientation questions (day of week, year, state)
• 5-item recall (immediate and delayed)
• Simple math problem
• Naming activity (The number of animals in 1-minute)
• Repeat number sequences backwards
• Clock draw
• Shape and size recognition
• Story/Reading comprehension [total of 8 points]

http://aging.slu.edu/pdfsurveys/mentalstatus.pdf
## SLUMS Scoring

<table>
<thead>
<tr>
<th></th>
<th>High School Education</th>
<th>&lt; High School Education</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>27-30</td>
<td>20-30</td>
</tr>
<tr>
<td>Mild Cognitive Impairment</td>
<td>20-27</td>
<td>14-19</td>
</tr>
<tr>
<td>Dementia</td>
<td>1-19</td>
<td>1-14</td>
</tr>
</tbody>
</table>

Maximum Score: 30

http://aging.slu.edu/pdfsurveys/mentalstatus.pdf
Clinical Course of Alzheimer’s

http://archiv.ethlife.ethz.ch/e/articles/sciencelife/alzheimerimpfung.html from R. Nitsch
Severity of Alzheimer’s

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Early Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Normal forgetfulness</td>
<td>• Reduced ability to perform job</td>
</tr>
<tr>
<td>• Subjective worry about memory loss is possible</td>
<td>• Increased difficulties with social interactions</td>
</tr>
<tr>
<td></td>
<td>• Deficit in memory or concentration</td>
</tr>
<tr>
<td></td>
<td>• Difficulty counting upwards by 7</td>
</tr>
</tbody>
</table>

## Severity of Alzheimer’s

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
</table>
| • Often function independently in many areas  
  • Ex: choosing proper clothing  
  • May need assistance with some areas to remain safe and increase independence  
  • May still be able to drive, work, and actively participate in some of their favorite activities | • For many this is the longest stage  
  • May have difficulties with:  
    • Routine tasks  
    • Personal hygiene  
    • Confused about location  
    • Begin wandering  
    • Difficulty counting to 10  
    • Some personality or behavioral changes; including suspiciousness, agitation, or obsessions  
    • Remote memory preserved | • Reduced communication  
  • Increased behavioral disturbances  
  • Motor dysfunction  
  • May become bed-bound  
    • Risk for DVTs, infections, aspiration pneumonia, decubitus ulcers  
  • Incontinence |

Theory of Retrogenesis

- Theory that stages of Alzheimer’s are correlated to developmental ages
- Humans of all ages need movement, socialization, love and dignity
- Theory that activities enjoyed by a person with Alzheimer’s would be similar to the types of activities at the similar developmental age

- Intergenerational programs – Daycares with an Adult Daycare

Living Situation & Stage of Dementia

- Home
- Assisted Living
- Nursing Home
A 71 yo WF is brought in by her husband because of concerns of worsening memory. She constantly repeats the same question despite him answering it. She has become suspicious that someone is breaking into their house and stealing her purse. You complete an MMSE and she scores a 16. Does she meet the criteria for:

A. Mild Cognitive Impairment
B. Mild-moderate Dementia
C. Moderate-severe Dementia
D. Severe Dementia
Based on her MMSE score today of 16 what would you recommend?

A. Watch and wait
B. Donepezil 5 mg PO daily
C. Rivastigmine 4.6 mg transdermal
D. Galantamine 4 mg PO BID
E. Donepezil 5 mg PO + Memantine 5 mg PO daily
## Alzheimer’s Dementia – FDA Approvals

<table>
<thead>
<tr>
<th></th>
<th>Mild-Moderate</th>
<th>Moderate-Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholinesterase Inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetylcholinesterase Inhibitors</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Donepezil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donepezil</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Galantamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Galantamine</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>X (PO, transdermal)</td>
<td>X (transdermal only)</td>
</tr>
<tr>
<td>NMDA-receptor antagonists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memantine</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Combination Product</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donepezil/Memantine</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

## Selecting Therapy for Alzheimer’s

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate/Severe</th>
</tr>
</thead>
</table>
| • Begin acetylcholinesterase inhibitor  
• Reevaluate in 2-4 weeks for adverse effects | • Begin acetylcholinesterase inhibitor ± memantine  
• If initially mild and deteriorates consider addition of memantine |

Evidence remains modest regarding efficacy of Acetylcholinesterase inhibitors (AChI) in mild to moderate Alzheimer’s Disease (AD) and memantine for moderate to severe AD.

Higher doses of donepezil did not show clinically meaningful benefit. Higher doses of transdermal rivastigmine may show greater benefit.

3 new trials of memantine in mild-moderate AD did not confer benefit. Newer trials show slight or unclear significance in adding memantine to AChI.

Newer long-term evidence regarding safety of AChI including anorexia, weight loss, falls, hip fractures, syncope, bradycardia, and increase pacemakers.
“Domino Trial” in 2012 of patients \([n = 295]\) with moderate to severe AD treated with donepezil for at least 3 months. 

Randomized to:

- Continue donepezil
- Switch to placebo (essentially d/c donepezil)
- Switch to placebo + memantine
- Continue donepezil and add memantine

**Results:**

- Continuation of donepezil saw ~32% less decline
- Discontinuation of donepezil saw a worsening of MMSE and Bristol Activities of Daily Living
- Those who discontinued donepezil but received memantine had less pronounced worsening (~20% decline)
- Those continued on donepezil and memantine was added conferred no additional benefit.

Howard R et al, NEJM 2012; 366(10):893-903
### Parkinson’s Dementia

<table>
<thead>
<tr>
<th></th>
<th>Mild-Moderate</th>
<th>Moderate-Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholinesterase Inhibitors (Cholinesterase Inhibitors)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>X (PO, transdermal)</td>
<td></td>
</tr>
</tbody>
</table>

Note some reports of memantine worsening hallucinations in PDD patients

Vascular Dementia

- 2016 Meta-Analysis
- 12 studies (mostly donepezil and galantamine; only n=2 rivastigmine)

Findings
- Donepezil 5 and 10 mg improved ADAs-Cog > placebo (difference in means -1.39 and -1.68, respectively; p≤ 0.008)
- Galantamine improved the ADAS-Cog > Placebo (difference in means -2.19, p<0.001)
- Rivastigmine did not show benefit on the ADAS-Cog
- None of the cholinesterase inhibitors showed improvement on the MMSE
- Treatment was associated with a 2-fold rate of discontinuation secondary to adverse events (OR 1.966, 95% CI 1.63-2.37. p <0.001)

Remember there is a high level of mixed pathology dementia – Vascular + Alzheimer’s

Lewy-Body Dementia

- Cholinesterase Inhibitors:
  - Some benefit in cognitive functions
    - Improved cognition, reduced fluctuations, increased alertness
  - Similar efficacy, donepezil most studied; galantamine least studied
  - May improve neuropsychiatric symptoms, reduce hallucinations

- Memantine
  - DLB or PDD patients treatment with memantine did better on the clinical global impression of change, but not on any other outcome measures
  - More recently a similar study DLB patients but not PDD patients improved with memantine

- Levodopa: may be used if severe motor symptoms, but can worsen psychiatric symptoms (hallucinations); DBL less responsive than patients with Parkinson’s disease

- Antipsychotics: paradoxical reaction; worsen motor functions – Generally AVOID

No medications are FDA approved for Vascular Dementia
Drugs in development:

- 5-HT$_6$ antagonist – intepirdine
  - Looking at change in cognitive symptoms and reducing parkinsonian symptoms
  - First released study showed no significant difference

- 5-HT$_2A$ inverse agonist - Nelotanserin
  - Assessing change in motor symptoms and visual hallucinations

- D1 receptor potentiator
- E2027 – phosphodiesterase-9 inhibitor

No medications are FDA approved for Vascular Dementia

Capouch SD, Neurol Ther 2018
Lack of studies

Non-pharmacologic preferred

SSRIs may be helpful for impulsivity, irritability, eating behavior, repetitive behaviors, and disinhibition
- Sertraline, fluvoxamine, citalopram and paroxetine

Trazodone doses of at least 300 mg/day over 12 weeks decreased problematic eating, agitation, irritability, dysphoria and depression

Stimulants – may improve cognitive functioning and lessen frontostriatal dysfunction and risk-taking behaviors, reduced disinhibition and apathy

Amantadine – may reduce repetitive and wandering behaviors

Cholinesterase inhibitors – have not shown benefit and may hasten cognitive decline and behavioral symptoms; this may be related to lack of role of cholinergic deficit in FTD

Memantine is FDA indicated for which stage of Alzheimer’s disease?

A. Mild cognitive impairment
B. Mild/moderate
C. Moderate/severe
D. Only in combination with donepezil for mild/moderate
SLEEP AND DEMENTIA
Up to 45% of Alzheimer’s Disease patients may have sleep disturbances

- Increased cognitive impairment
- Nighttime behavioral disturbances (wandering, repeatedly getting up during the night, hallucinations, day/night confusion) can increase caregiver burden
- Can ultimately increase risk/worsen behavioral disturbances
- Changes in sleep architecture can be more severe than normal for age
- Sleep related breathing disorder is seen more frequently in Alzheimer’s patients ranging from 40-70%
  - May be related to cognitive decline at an earlier age

- Lewy Body Dementia associated with REM sleep behavior disorder

Nat Sci Sleep Jan 2016:8:21-33
H/O sleep disordered breathing is a risk for all-cause dementia, Alzheimer’s and vascular

Whereas insomnia increased the risk of Alzheimer’s but not vascular or all-cause dementia
Insomnia

- Usually characterized by difficulty:
  - Falling asleep
  - Staying asleep
  - Early morning awakening

- Feel tired the next day...
Non-pharmacologic Treatments for Sleep Disturbances in Dementia

- Regular exercise
  - Promotes relaxation
- Bright light therapy
  - Managing insomnia in dementia

BEERS UPDATES – SEDATIVE/HYPNOTICS

<table>
<thead>
<tr>
<th>Drug/Drug Class</th>
<th>2002</th>
<th>2012</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine</td>
<td>AVOID</td>
<td>AVOID</td>
<td>AVOID</td>
</tr>
<tr>
<td>TCAs</td>
<td>AVOID tertiary amines (e.g. doxepin, amitriptyline)</td>
<td>AVOID all tertiary amines except doxepin doses ≤ 6 mg (OK)</td>
<td>AVOID all tertiary amines except doxepin doses ≤ 6 mg (OK)</td>
</tr>
<tr>
<td>Benzodiazepines (BZD)</td>
<td>AVOID long-acting Use lower doses of short acting (temazepam ≤15 mg; triazolam ≤ 0.25 mg)</td>
<td>AVOID all BZDs for insomnia</td>
<td>AVOID</td>
</tr>
<tr>
<td>Non-BZD – “Z” hypnotics</td>
<td>Not mentioned</td>
<td>Avoid chronic use ≥ 90 days</td>
<td>AVOID; risk similar to BZDs</td>
</tr>
</tbody>
</table>

Long-acting benzodiazepines: flurazepam, quazepam, estazolam  
“z” hypnotics include eszopiclone, zaleplon and zolpidem
NONE
**Antidepressants**
- Doxepin 3 – 6 mg at bedtime – FDA approved was actually studied in the elderly and did not increase anticholinergic effects at low doses
- Off-label - trazodone 25 – 100 mg at bedtime – Monitor for additive orthostatic hypotension

**Melatonin receptor agonists:**
- Ramelteon 8 mg at bedtime

**Orexin Antagonists:**
- Suvorexant was studied in elderly; however at 15-30 mg

- **OTC melatonin**
  - Recommend taking a few hours before desired bedtime
Benzodiazepines

Which benzodiazepine is preferred in the elderly if indicated?

**Pros:** Anxiolytic effects; sedating; cost

**Cons:** FALLS!, Potential for abuse; adverse effects; rebound insomnia (triazolam); amnestic properties (triazolam); only indicated for short-term use; on the Beers list of potentially inappropriate medications for elderly; prolonged half-life with flurazepam and quazepam; next-day sedation, may worsen cognitive impairment

flurazepam, estazolam, quazepam, triazolam, temazepam
“Z” Hypnotics

**Pros:** Most prescribed sleep aids; eszopiclone and zolpidem CR studied for long-term use

**Cons:** Potential for abuse; adverse effects; sleep-related behaviors; next-day sedation; next-day driving impairment; on Beers list; falls with injury

Zolpidem can cause drowsiness and a decreased level of consciousness, which may lead to falls and consequently to severe injuries. Severe injuries such as hip fractures and intracranial hemorrhage have been reported.

Note
Zolpidem products only!
Flurazepam does list risk of falls

Zolpidem prescribing information
**Ramelteon**

**Pros:** Potentially less next day sedation, no abuse potential, less balance adverse effects

**Cons:** Drug interactions with CYP1A2 inhibitors (e.g., ciprofloxacin, fluvoxamine); cost; patient perception of effectiveness; only approved for sleep onset not sleep maintenance

**Suvorexant**

**Pros:** Unique mechanism of action → does not work on GABA$_A$; helps with both sleep onset and sleep maintenance; was studied in elderly patients (up to 30 mg)

**Cons:** Controlled substance; newer medication; cost; role in therapy not defined/established; no head-to-head trials with GABA agents; doses in original studies were higher than doses approved for insomnia; potential safety concerns, rare narcolepsy-like effects, should not drive with doses of 20 mg

**Sedating Antidepressants**

**Pros:** low-dose doxepin, FDA approved, studied in elderly, lacks anticholinergic effects at low doses. Trazodone and mirtazapine beneficial with comorbid depression, no potential for abuse, less next-day hangover effects

**Cons:** orthostasis with trazodone, weight gain with mirtazapine. For off-label antidepressants minimal evidence in non-depressed population

**FDA approved:** doxepin 3-6 mg

**Off-label:** trazodone, mirtazapine
Melatonin

• **Pros:** Among the supplements, it has the most promising evidence; helps with circadian rhythm disorders (e.g., jet lag), delayed sleep phase syndrome, patients with low endogenous melatonin levels, growing role in REM sleep-behavior disorder

• **Cons:** As an herbal, it is not regulated by FDA; CYP1A2 drug interactions

• **If you were to consider:**
  Recommend melatonin doses ranging from 0.5-10 mg have been recommended; most patients need only 1-3 mg
REM Sleep Behavior Disorder

- Age of onset 40 – 70 years of age
- 0.5% Incidence
- Symptoms: Act out their dreams (talking, flailing, punching, kicking, etc..); almost never walk; eyes are closed
- Associated with:
  - Parkinsonism and Parkinson’s disease (REM sleep disorder may be prodromal to PD)
  - Cognitive dysfunction – Lewy-body Dementia (76% post-mortem confirmed DLB) and Parkinson’s Dementia
  - Multi-system atrophy
  - Narcolepsy
- Consequences: harm to bed partner, self-injury, bone fractures

Mortality may be sooner in DLB with REM-BD; In patients where REM-BD preceded the dementia, may die even earlier.
REM Sleep Behavior Disorder

- Treatment options:
  - Clonazepam
    - Traditionally considered first-line
    - Beers Criteria does recognize that it may be appropriate in REM sleep disorders
  - Melatonin
    - Becoming favored as first-line
    - 2015 review of the evidence found some small evidence reducing REM sleep without atonia in one placebo-controlled trial (n=4) and two open-label trials (n=6, n=15)
    - Dose up to 15 mg
  - Modafinil/Armodafinil
    - Small 12-week open label study improved wakefulness

Sundowning

- Correlation of worsening behavioral symptoms in the late afternoon/early evening
- Cochrane Review identified 4 studies
  - melatonin = 2, ramelteon = 1, trazodone = 1
  - Conclusion: Lack of evidence to help guide drug therapy in managing sleep disturbances in AD
- Risk versus benefit of low-dose antipsychotic
Wandering Behavior

- Currently no medication therapy exist
- Non-pharmacologic – Exercise; take a short walk
- Devices – more research is being put into tracking devices; global track devices, barcodes
  - Major drawbacks: cost, ethics, privacy

**Antipsychotics – “off-label”**

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Pros</th>
<th>Cons</th>
<th>Dosing</th>
<th>Maximum in dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>Sedating, less weight gain than olanzapine</td>
<td>More EPS, orthostasis, metabolic</td>
<td>0.25-0.5 mg at bedtime or BID</td>
<td>2 mg/day</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Sedating, less EPS</td>
<td>Orthostasis, metabolic, paucity of data for insomnia, weak antipsychotic</td>
<td>12.5-25 mg at bedtime up to TID</td>
<td>200 mg/day</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Sedating</td>
<td>Very anticholinergic, more metabolic</td>
<td>2.5-5 mg at bedtime</td>
<td>? 5 -10 mg/day</td>
</tr>
</tbody>
</table>

Black-box warning on ALL antipsychotics: Increased risk of DEATH in patients with dementia-related psychosis → 4.6% (antipsychotic treated) vs. 2.6% (placebo). Related to cardiovascular or infectious causes.
1. Alzheimer’s is the most common type of dementia, other types of dementia include vascular, lewy-body, and fronto-temporal

2. Dementia is a progressive disease and worsens in severity over time

3. Cholinesterase inhibitors are only approved for Alzheimer’s and Parkinson’s dementia, but may be used off-label in other forms of dementia; but may actually worsen symptoms in fronto-temporal dementia

4. Sleep disorders are prevalent in dementia, non-pharmacologic strategies should be employed first; and risk versus benefit of medications should be weighed before starting pharmacotherapy
Rapid-eye movement (REM) sleep behavior disorder is associated with which type of dementia?

A. Alzheimer’s
B. Vascular
C. Lewy-body
D. Fronto-temporal
Which of the following is a risk associated with use of zolpidem in elderly patients?

A. Falls with injury
B. Decreased appetite
C. Cognitive Impairment
D. Anticholinergic effects