UVM Project ECHO:
Enhanced Diagnosis and Management of Dementia by the Primary Care Team

May 19, 2022

Course Co-Directors: Mary Val Palumbo, DNP, APRN, GNP-BC
                      John Steele Taylor, MD

ECHO Director:      Elizabeth Cote

Series Faculty:     John Coffin, MSW
                    Allegra Miller, M.Ed, Family Caregiver
                    Heather Zuk, OTR, CDRS, CDI
                    Tiffany Smith, MA, CRTS, CDP
                    Lori McKenna, MSW, LICSW
                    Jackie Rogers, PhD
                    Zail S. Berry, MD, MPH
                    Doug Franzoni, PharmD, BCGP
                    Michael LaMantia, MD (UVM Geriatric Services)
                    Amelia Gennari, MD (UVM Geriatric Services)
• RECORDING OF SESSION TO BEGIN
Agenda

• Introductions
• Objectives
• Didactic Presentation (~20-30 min)
• Case presentation
  • Clarifying questions
  • Participants – then faculty panel
• Discussion
• Recommendations
• Summary
• Closing Announcements
  • Submission of new cases
  • Completion of evaluations
Series Objectives

Learning objectives for this ECHO series include being able to:

• Describe current standard of care for diagnosis, treatment, and care of patients with cognitive impairment, Alzheimer’s disease (AD), and dementias – evidence-based review and approaches.

• Name non-pharmacological resources for family caregivers including caregiver supports and assistance in management of caregiver stress.

• List pharmacologic approaches to sleep and behavioral issues.

• Discuss side effects of pharmacologic approaches to sleep and behavioral issues.

• Identify Vermont-specific rules regarding driving and guardianship.
CME Disclosures

University of Vermont (UVM) Office of Continuing Medical and Interprofessional Education (CMIE) is approved as a provider of Continuing Medical Education (CME) by the ACCME. UVM designates this internet live activity for a maximum of 1.5 AMA PRA Category 1 Credits. Participants should claim only the credit commensurate with the extent of their participation in the activity.
CME Disclosures

**Interest Disclosures:** As an organization accredited by the ACCME to sponsor continuing medical education activities, UVMCMIE is required to disclose any real or apparent conflicts of interest (COI) that any speakers may have related to the content of their presentations.

**Meeting Disclaimer:** Regarding materials and information received during this educational event, the views, statements, and recommendations expressed during this activity represent those of the authors and speakers and do not necessarily represent the views of the University of Vermont.
Managing Behavioral Problems and Sleep Pharmacological Approaches

Doug Franzoni, PharmD, BCGP
UVMMC Ambulatory Pharmacy Supervisor
Consulting Geriatric Pharmacist

[I have no conflicts to disclose.]
Managing Behavioral Problems and Sleep Pharmacological Approaches

Session Objectives:

1. Exploring primary pharmacological treatments for behavioral problems associated with dementia.

2. Understanding the limitations of pharmacological interventions with neuropsychiatric symptoms of dementia.

3. Gain a better understanding of the prescribing nuances associated with the respective drug classes.
Behavioral Issues

• **Examples:**
  • Agitation
  • Aggression
  • Paranoia
  • Depression
  • Delusions
  • Hallucinations

★ *Sleep disturbances*

• Sundowning feature

• ALWAYS rule out underlying cause before grabbing a pharmacological agent
  • Is it another medication?
    • Anticholinergic burden

[Diagram showing the relationship between unfamiliar surroundings, loud noises, frantic environment, difficulty with tasks, inability to communicate, and physical discomfort.]

https://www.helpguide.org/articles/alzheimers-dementia-aging/alzheimers-behavior-management.htm
Linking the Drug to a Behavior
Agitation and Aggression

• **Acetylcholinesterase Inhibitors**
  • Statistically small improvement in behaviors
    • DLB>AD
    • Pts were all considered mild to moderate degrees of dementia
  • **Clinical Pearls**
    • No dose adjustment needed (hepatic or renal)
    • Time to steady state = 15 days
    • Not indicated for vascular dementia unless mixed presentation
    • GI ADEs - transdermal has less risk but higher cost

• **NMDA receptor antagonist**
  • Did NOT show a clinically significant effect on neuropsychiatric symptoms of dementia

• **SSRIs**
  • Specifically *citalopram* at doses of 10-20mg daily
  • **Clinical Pearls**
    • QTc prolongation
    • Sertraline a better alternative if this is a concern
    • MDD for pts >60y/o = 20mg
    • SIADH

• **Other Agents**
• Refractory Symptoms

  • Antipsychotics
    • Key principals
    • Goals of care
      • At what point do you use?
    • Primary choice is atypical antipsychotics
    • Limitation of most primary literature data
## Linking the Drug to a Behavior
### Agitation and Aggression

<p>| Selected adverse effects of antipsychotic medications for schizophrenia(^{[1,2]}) |
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<th>Akathisia</th>
<th>Parkinsonism</th>
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https://www.uptodate.com/contents/second-generation-antipsychotic-medications-pharmacology-administration-and-side-effects?search=antipsychotics&source=search_result&selectedTitle=2~146&usage_type=default&display_rank=1
Antipsychotic clinical pearls

- ADEs will likely be the deciding factor for what agent you should use
- Patients with dementia with Lewy body may be more sensitive to antipsychotics and thus, conservative dose titration is recommended

Mortality risk

- Overall increase risk of stroke, MI and death — particularly those with vascular disease
- Increase in odds ratio is 1.5-1.7
- Increase absolute risk of death is 1 to 2%
- Higher for first gen antipsychotics
Linking the Drug to a Behavior

Depression

- SSRIs are the drug of choice
  - Favor citalopram over sertraline
    - Citalopram saw benefit after 24 weeks during two multi center trails
    - Sertraline showed no difference
  - Possible role of bupropion and venlafaxine
  - No benefit seen with mirtazapine
- Apathy Tx
  - SSRI with or without methylphenidate
    - Trial showed improved apathy scores when used in combo
      - Improvement also seen in depression
    - Start at very low dose to minimize worsening sleep
Sleep Changes

• Total sleep time decreases by 30 minutes per decade starting in mid-life

• Sleep becomes increasingly lighter and fragmented with age

• Overall time and episodic time spent in REM decreases

• Circadian rhythm change
  • Phase advancement

https://medlineplus.gov/ency/article/000064.htm
Dementia Related Sleep Changes

• Bidirectional relationship

• Comparably more disruptive sleep when compared to age-matched controls

• Overall more severe changes in sleep architecture
Dementia Related Sleep Changes  
**AD & PD & DLB**

- *Parkinson disease (PD) and dementia with Lewy bodies (DLB)*
  - Nighttime sleep disturbances early in the disease and stable throughout
- *Alzheimer disease (AD)*
  - Prominent in later stages of the disease

- Longer awakening
- Increase in stage 1 sleep and decrease in deep sleep
- Decrease % of REM and number of episodes
- Increase in phase delay
- Dysregulation of melatonin secretion
- Circadian rhythm changes
- Excessive daytime sleepiness
Initial Approach

• Rule out other medication side effects
  • Consider timing of medication administration
• Evaluate and treat underlying causes
• Environmental factors
• Sleep hygiene
• Increase in social stimulation during the day
• CBT
Pharmacological Approach
Category Breakdown

- Meds indicated for Insomnia for *adults*
  - Benzodiazepine receptor agonist (BZRAs)
  - Nonbenzodiazepine BZRAs
  - Dual orexin receptor antagonist
  - Histamine receptor antagonist
  - Melatonin receptor antagonist
- Off-label meds commonly prescribed
  - Trazodone
  - Mirtazapine
  - Amitriptyline
- OTC
  - Diphenhydramine & Doxylamine
- Dietary supplements
  - Melatonin

- Meds indicated for Insomnia for *older adults and adults with dementia*
  - Benzodiazepine receptor agonist (BZRAs)
  - Nonbenzodiazepine BZRAs
  - Dual orexin receptor antagonist
  - Histamine receptor antagonist
  - Melatonin receptor antagonist
- Off-label meds commonly prescribed
  - Trazodone
  - Mirtazapine
  - Amitriptyline
- OTC
  - Diphenhydramine & Doxylamine
- Dietary supplements
  - Melatonin
Meds indicated for Insomnia for adults with dementia
Dual Orexin Receptor Antagonist

• MOA - blocks the binding of wake-promoting neuropeptides orexin-A and orexin-B to receptors OX1R and OX2R which is thought to suppress wake drive

• FDA indication for insomnia with difficulty of both sleep onset and maintenance

• Kinetics
  • 3A4 substrate
  • Highly protein bound

• Controlled substance (C-IV)
• Brand Only — Issue for many PBMs
**Meds indicated for Insomnia for adults with dementia**

**Dual Orexin Receptor Antagonist**

<table>
<thead>
<tr>
<th>SEDATIVE/HYPNOTICS</th>
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<td><strong>BENZODIAZEPINE</strong></td>
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<tr>
<td>ESTAZOLAM</td>
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<td>TEMAZEPAM 15 mg, 30 mg (compare to Restoril®)</td>
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<tr>
<td>Flurazepam Halcion® (triazolam)</td>
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<td>Restoril® (temazepam)</td>
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<tr>
<td>Temazepam 7.5 mg, 22.5 mg (compare to Restoril®)</td>
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<td>Triazolam (compare to Halcion®)</td>
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<tr>
<th><strong>NON BENZODIAZEPINE, NON BARBITURATE</strong></th>
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<td>ESZOPICLONE (compare to Lunesta)</td>
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<td>ZALEPLON</td>
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<td>QTY LIMIT: 5 mg = 1 cap/day, 10 mg = 2 caps/day</td>
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<td>ZOLPIDEM (compare to Ambien®)</td>
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<td>QTY LIMIT: 1 tab/day</td>
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<td>Ambien® (zolpidem)</td>
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<td>Ambien CR® (zolpidem)</td>
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<td>Belsomra® (suvorexant)</td>
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<td>Ramelteon (compare to Rozerem®)</td>
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<td>Rozerem® (ramelteon)</td>
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**Criteria for Approval:** The patient has had a documented side effect, allergy, or treatment failure with two preferred benzodiazepine sedative/hypnotics. If a product has an AB rated generic, one trial must be the generic.

Ambien, Lunesta: The patient has had a documented intolerance to the generic equivalent.

Ambien CR, Belsomra, Zolpidem CR: The patient has had a documented side effect, allergy or treatment failure to two preferred sedative/hypnotics and Belsomra.

Dayvigo: The patient has had a documented side effect, allergy, or treatment failure to two preferred sedative/hypnotics and Belsomra.

Edluar: The patient has a medical necessity for a disintegrating tablet formulation (i.e. swallowing disorder).

Intermezzo: The patient has insomnia characterized by middle-of-the-night awakening followed by difficulty returning to sleep AND The patient has had a documented inadequate response to two preferred sedative/hypnotics.

Ramelteon, Rozerem: The patient has had a documented side effect, allergy, contraindication, or treatment failure to one preferred sedative/hypnotic OR the patient has had a treatment failure after a minimum 2-week trial of melatonin.

Meds indicated for Insomnia for adults with dementia
Dual Orexin Receptor Antagonist

- 2 Trials: Herring 2020 & NCT03001557
- Cochrane analysis looked at all 323 patients between the two studies

- Moderate-certainty evidence showed:
  - Increase in total nocturnal sleep time with suvorexant
  - Decrease in nocturnal time awake with suvorexant
  - No effect on number of nocturnal awakening
  - No higher risk of ADEs compared to placebo
Meds indicated for Insomnia for adults with dementia

Trazodone

• MOA - Inhibits reuptake of serotonin (5-HT), antagonizes 5HT2a and induces significant changes in 5-HT presynaptic receptor adrenoreceptors. Significantly blocks histamine (H1) and alpha1 adrenergic receptors.

• FDA indication for unipolar MDD

• Black Box warning for suicidal thoughts and behaviors

• QTc prolongation

• Kinetics
  • 3A4 substrate
  • Highly protein bound
  • Time to peak is about 30-100min but can be delayed up to 2.5 hrs with food
  • Half-life increase in obese patients
Meds indicated for Insomnia for adults with dementia

**Trazodone**

- Camargos 2014
  - Trazodone 50mg at night vs placebo
  - Parallel group study
  - 30 outpatients with moderate to severe dementia
  - Overall outcomes considered low-certainty given very imprecise methodology
  - Possibly benefit of decrease in time spent awake after sleep initiated
  - All ADEs were mild and similar in frequency between the study groups
**Meds indicated for Insomnia for adults with dementia**

*Ramelteon & Melatonin*

- MOA - melatonin receptor agonist at the MT1 and MT2 receptors
- FDA indication for sleep onset
- Kinetics
  - Extensive first-pass effect
  - Onset of action is 30 min, peak is 1.5 hours
  - AUC is 97% higher and Cmax is 86% higher when compared between older and younger adults
Meds indicated for Insomnia for adults with dementia
Ramelteon & Melatonin

• Cochrane library analysis on 4 studies for melatonin
  • Patients ranged from moderate to severe dementia and were both in the community and resident in long-term care facilities
  • Doses ranged from 2mg to 10mg of varying release forms
  • Patents were followed over 8 to 24 weeks
  • No difference seen between melatonin and placebo for:
    • Total sleep time, daytime to nighttime sleep ratio, MMSE score and ADLs
  • Ramelteon trial NCT00325728
Meds indicated for Insomnia for adults with dementia
Mirtazapine

• Minimal primary literature
  • Most trials looks at insomnia or sleep disturbances in patients with major depressive disorder
  • May have a place in neuropsychiatric symptoms of dementia, just not with regards to sleep

• Clinical pearls
  • Long half-life
  • Increased appetite & weight gain
Sources


Discussion and Q & A
The discussion and materials included in this conference are confidential and privileged pursuant to 26VSA Section 1441-1443. This material is intended for use in improving patient care. It is privileged and strictly confidential and is to be used only for the evaluation and improvement of patient care.
Case Presentation Format

Case presentation from a participant (a real-world case, from the field)
Then
Clarifying questions about the case from group to case presenter
Then
Ideas, suggestions, recommendations from participants
Then
Ideas, suggestions, recommendations from ECHO faculty team
Then
Additional discussion, if any (All)
Then
Summary of case discussion
(course co-directors: Mary Val Palumbo, DNP, APRN, GNP-BC and John Steele Taylor MD)
• RECORDING TO BE STOPPED FOR CASE PRESENTATION
Questions and Discussion from the group....
Dementia Clinical Consults
45 min slots available
2nd and 4th Wednesdays
2-4 PM
Sign up at: https://www.signupgenius.com/go/5080B4AAACAE2F6FC1-corner

Or Email:
Mary.Palumbo@med.uvm.edu

Diagnosis & Management of Dementia
For Primary Care and other healthcare providers.

Online Learning via Vermont Health Learn
(CMEs at your own pace)
Register at https://catalog.ythl.org/product?catalog=Dementia-Diagnosis-Treatment-Management
Conclusion

• Slides are posted at www.vtahec.org

• Volunteers to present cases (this is key to the Project ECHO model)
  • Please submit cases to Mary.Palumbo@med.uvm.edu

• Please complete evaluation survey after each session

• Once your completed evaluation is submitted, CE information will be emailed to you.

• Please contact us with any questions, concerns, or suggestions
  • Mary.Palumbo@med.uvm.edu
  • Elizabeth.Cote@uvm.edu