Evaluation and Management of Agitation and Aggression in Dementia
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Objectives

• Differentiate between delirium, terminal restlessness, and dementia related agitation and aggression
• Identify and treat contributors to agitation and aggression in dementia
• Implement effective non-pharmacologic management approaches to agitation and aggression in dementia
• Incorporate pharmacologic treatment strategies to manage agitation and aggression in dementia

Background: Dementia Epidemiology

• Current estimate: 5.1 million in US (ADAMS Study)
  • 3.2 million women
  • 1.8 million men
• Projected for 2050: 14 million
• 1 in 3 women will develop dementia during her lifetime
• Almost 1/3 of people over age 85 have dementia
• Someone new develops dementia every 67 seconds in the US

Alzheimer's Association at https://www.alz.org/alzheimers_disease_facts_and_figures.asp
Background: Dementia End of Life

- 1 in 3 older adults who die each year have a diagnosis of dementia
- Diagnosis of dementia cuts ones life expectancy in half
- 5th leading cause of death in persons over the age of 65
- >500,000 dementia deaths per year in US attributed to dementia

Alzheimer’s Association. Available at https://www.alz.org/alzheimers_disease_facts_and_figures.asp

Hospice Use by Primary Diagnosis

- Health Affairs 2017

Symptoms End Stage Dementia

Agitation and Aggression in Dementia and Health Related Outcomes

- **Patient**
  - Increased morbidity and mortality
  - Increased likelihood of hospitalization and longer length of stay
  - Early placement in a nursing home

- **Caregiver**
  - Stress and strain
  - Depression and anxiety
  - Reduced income from employment
  - Lower quality of life.

- **Behaviors and their management contribute to 1/3 of total dementia-related costs**

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**Case 1:**

61 y/o with Huntington’s who presents to the IPU with impulsivity and agitation—not slept in 2 days, more confused, pacing, eating food out of garbage. Patient recently admitted to hospice with functional decline, falls, weight loss, dysphagia, and worsening behaviors. Interventions to date: Haldol 5mg every 6 hours and every 2 hours as needed, mirtazapine 30mg at night, sertraline 50mg daily, lorazepam 1mg every 6 hours and 1 hour as needed, amantadine 200mg daily. Urinalysis and bloodwork were unremarkable. Patient transferred to the IPU for further management of impulsivity and agitation.

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**Case 2:**

86 y/o with cerebral atherosclerosis with recent functional decline and in past 2 weeks bedbound, fall, stage II sacrum, poor appetite and weight loss, and increased agitation/aggression. Daughter took patient out of ALF after hitting and trying to bite several staff. She spends most of the day yelling and swearing, kicking, and very restless in bed. Comorbidities: hard of hearing, poor vision, arthritis, peripheral vascular disease, history of stroke, hypertension, depression, and HF. Patient admitted to hospice and transferred to the IPU for management of vocalizations and agitation/aggression. Medications sertraline 100mg daily. Bloodwork and urinalysis were unremarkable.
Guiding Principles

- Identify dementia etiology as symptoms and treatments vary
- Differentiate delirium, terminal restlessness, and dementia related agitation
- Evaluate and manage all contributors to agitation
- Identify the target symptoms to be treated and characterize impact on patient and or caregiver
- Non-pharmacologic interventions
  - Person-centered
  - Caregiver
  - Environment
- Pharmacologic treatment

Most Common Etiologies of Dementia in US

<table>
<thead>
<tr>
<th>Dementia Diagnosis</th>
<th>Relative Frequency</th>
<th>Pathophysiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s disease</td>
<td>35-55%</td>
<td>amyloid plaques and neurofibrillary tangles</td>
</tr>
<tr>
<td>Mixed-vascular and Alzheimer’s disease</td>
<td>25-35%</td>
<td>Combination of Alzheimer’s disease and vascular disease</td>
</tr>
<tr>
<td>Lewy Body Dementia</td>
<td>0-30%</td>
<td>alpha-synuclein protein</td>
</tr>
<tr>
<td>Vascular Dementia</td>
<td>10-20%</td>
<td>cortical infarcts, subcortical infarcts, and leukoaraiosis</td>
</tr>
<tr>
<td>Frontotemporal Dementia</td>
<td>&lt;5%</td>
<td>Tau protein</td>
</tr>
</tbody>
</table>

Dementia Etiology Considerations

- Depression is more common in vascular dementia
- Hallucinations seen more often in Lewy body dementia
  - Special consideration ACEI and antipsychotics
- Frontotemporal dementia often exhibit executive control loss
  - Disinhibition
  - Wandering
  - Social inappropriateness
- Apathy
- Agitation and aggression increase in frequency with all conditions with disease progression
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Delirium: Definition


Terminal Restlessness
Dementia Related Agitation and Aggression

- Agitation
- Purposeless hyperactivity
- Verbal or physical aggression
- Impulsiveness
- Resisting care
- Repetitive behavior
- Wandering

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Contributors to Agitation

<table>
<thead>
<tr>
<th>Contributor</th>
<th>Causes</th>
<th>Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Symptom</td>
<td>Pain, SOB</td>
<td>Opioid</td>
</tr>
<tr>
<td>Psychological symptom</td>
<td>Depression, Anxiety</td>
<td>SSRI, SNRI CBT</td>
</tr>
<tr>
<td>Medical Illness</td>
<td>Delirium, infection, constipation</td>
<td>Treat condition</td>
</tr>
<tr>
<td>Unmet Need</td>
<td>Hunger, thirst, cold</td>
<td>Attend to need</td>
</tr>
<tr>
<td>Sensory impairment</td>
<td>Poor vision/heatin</td>
<td>Adaptive</td>
</tr>
<tr>
<td>Environment</td>
<td>Under/over stimulation</td>
<td>Modify</td>
</tr>
<tr>
<td>Pharmacologic</td>
<td>Dig, caffeine, benzos</td>
<td>Discontinue</td>
</tr>
<tr>
<td>Dementia</td>
<td>AD, Mixed, LBD</td>
<td>Ach/EI</td>
</tr>
</tbody>
</table>
Pain and Behavioral Disturbances in Dementia-NH

Behavioral Disturbances by Intervention

FDA Approved Medications Used to Treat Dementia

<table>
<thead>
<tr>
<th>Medication</th>
<th>Severity</th>
<th>Dose</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil (Aricept)</td>
<td>Mild to severe</td>
<td>5-10mg; 23mg</td>
<td>*Nightmares</td>
</tr>
<tr>
<td>Rivastigmine (Exelon)</td>
<td>Mild to moderate</td>
<td>4.6 &amp; 9.5mg (13mg patch)</td>
<td>*Weight loss</td>
</tr>
<tr>
<td>Galantamine (Razadyne)</td>
<td>Mild to moderate</td>
<td>8-24mg</td>
<td>*</td>
</tr>
<tr>
<td>Memantine (Namenda XR)</td>
<td>Moderate to severe</td>
<td>28mg QD</td>
<td>Constipation, dizziness, HA</td>
</tr>
</tbody>
</table>

*Cholinesterase inhibitors: Nausea, vomiting, diarrhea, dizziness
Guiding Principles

- Identify dementia etiology as symptoms and treatments vary
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**Non-pharmacologic interventions**

- Person-centered
- Caregiver
- Environment
- Pharmacologic treatment

Non-Pharmacologic Treatment Agitation and Dementia

- Unmet need- behavior as an underlying need
  - agitation etiology, remaining abilities, level of cognitive functioning, and past/present interests
- Learning and behavioral (ABC)
  - behavior consequence reinforces behavior
- Environmental vulnerability and reduced stress thresholds: a mismatch between the setting and the patient’s ability to deal with it.

Non-Pharmacologic Approaches

• Persons with dementia
• Caregivers
• Environment

Non-Pharmacologic Persons with Dementia: Inconclusive

• Reminiscence therapy (discussion of past experiences)
• Validation therapy (working through unresolved conflicts)
• Simulated presence therapy (use of audiotaped recordings of family members' voices)
• Aromatherapy (use of fragrant plant oils)
• Snoezelen (placing the person with dementia in a soothing and stimulating environment known as a "snoezelen room")
• Cognitive training and rehabilitation
• Acupuncture
• Light therapy

Non-Pharmacologic Persons with Dementia 2: Evidence exists 2 or more RCTs

• Physical activity- better with depression and sleep
• Hand massage
• Personalizing the bathing experience
Non Pharmacologic Caregivers: Most Robust Evidence

- Problem solving with a family care giver
  - Identify precipitating and modifiable causes of symptoms
  - Efforts to modify these causes with selected non-pharmacologic strategies
- Example Programs
  - REACH II and REACH VA: Coping approaches and tailored behavioral management
  - The Tailored Activity Program (TAP): Occupational Therapy
  - The Advancing Caregiver Training (ACT): Health Professionals
- A meta-analysis of 23 randomized clinical trials, involving almost 3300 community dwelling patients and their care givers
  - Significantly reduced behavioral symptoms (effect size 0.34, 0.20 to 0.48).
  - Similar to antipsychotics for behavior and cholinesterase inhibitors for memory

Non-Pharmacologic Environment: Few RCTs, positive impact

- Overstimulation (for example, excess noise, people, or clutter in the home)
- Understimulated (for example, lack of anything of interest to look at)
- Safety problems (for example, access to household chemicals or sharp objects or easy ability to exit the home)
- Lack of activity and structure (for example, no regular exercise or activities that match interests and capabilities)
- Lack of established routines (for example, frequent changes in the time, location, or sequence of daily activities).

Responses to Non-Pharmacologic Interventions

Greater Response
- Higher levels of cognitive function
- Fewer difficulties with ADLs
- Speech
- Communication
- Responsiveness

Less Response
- Staff barriers (refuse to participate)
- Patient in pain

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Pharmacologic Treatment Themes

- Lack of consistent terminology and definition
  - Neuropsychiatric symptom
  - Behavioral and psychological symptom
  - Descriptive terms
- Heterogeneity of measures
  - CMAI
  - NPI
- Studies of limited size and quality
- Conflicting or weak evidence base

Pharmacologic Treatment of Agitation

<table>
<thead>
<tr>
<th>Therapeutic Class</th>
<th>Trial</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trazodone</td>
<td>+ RCT</td>
<td>Sedation, Hypotension</td>
</tr>
<tr>
<td>SSRI (citalopram)</td>
<td>+ RCT</td>
<td>Nausea, diarrhea, OR (60mg daily and higher)</td>
</tr>
<tr>
<td>Dextromethorphan/quinidine</td>
<td>+ RCT</td>
<td>Falls, dizziness, diarrhea, UTIs</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>+ RCT</td>
<td>Sedation, falls, shivers, agitation</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>+ RCT</td>
<td>Nausea, infection, or QTc prolongation, DM, death...</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>-RCT</td>
<td>Sedation, anemia, liver toxic</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>-RCT</td>
<td>Liver toxic, sedation</td>
</tr>
<tr>
<td>NMDA antagonist</td>
<td>-RCT</td>
<td>Nausea, dizziness</td>
</tr>
<tr>
<td>AChE inhibitor</td>
<td>-RCT</td>
<td>Nausea, dizziness, weight loss</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>-RCT</td>
<td>Low dose used, oral form</td>
</tr>
</tbody>
</table>

Trazadone

- Several small randomized controlled trials indicate benefit
  - Cochrane review inconclusive evidence
- Dosing: 25-50mg BID-TID, maximum dose 400mg-600mg
- Adverse effects:
  - Orthostasis, syncope, hypotension, dizziness
  - Priapism
  - SIADH
  - Somnolence
  - QTc prolongation

Citalopram for Agitation in Alzheimer’s Disease

Citalopram Considerations

- QTc prolongation which is dose dependent
- Starting dose 10mg up to 40mg daily
- Consider twice daily dosing
  - 10mg daily for two weeks
  - 10mg twice daily thereafter
- Other SSRl side effects
- Onset of action within a week in one study
Dextromethorphan-Quinidine For Dementia Agitation in Alzheimer’s Disease

- FDA approved for the treatment of pseudobulbar affect
- Modulates glutamate, serotonin, and norepinephrine
- Only one randomized controlled trial to date for agitation
- Side effects include
  - Falls
  - UTIs
  - Diarrhea
  - Dizziness
  - QTc prolongation

Anxiolytics

- Binds to GABA receptor in CNS
- Anxiolytic, sedative, and hypnotic effects (anterograde memory)
- Increased risk of adverse events
  - Falls
  - Cognitive impairment / confusion
  - Hip fracture
  - Sedation
  - Paradoxical agitation
Pharmacology Common Agents

<table>
<thead>
<tr>
<th>Benzodiazepine</th>
<th>Half-life</th>
<th>Dosage range</th>
</tr>
</thead>
<tbody>
<tr>
<td>diazepam</td>
<td>20-50 hours</td>
<td>2-10mg</td>
</tr>
<tr>
<td></td>
<td>Over 100 OA</td>
<td></td>
</tr>
<tr>
<td>lorazepam</td>
<td>12 hours</td>
<td>0.5-2mg</td>
</tr>
<tr>
<td>alprazolam</td>
<td>16 hours</td>
<td>0.25-3mg</td>
</tr>
<tr>
<td></td>
<td>(9-27 range)</td>
<td></td>
</tr>
<tr>
<td>clonazepam</td>
<td>30-40 hours</td>
<td>0.25-5mg</td>
</tr>
</tbody>
</table>

Agitation and Dementia: Lorazepam

Antipsychotics

- Best-studied pharmacologic intervention for dementia-related agitation
- Moderate efficacy across trials and agents
  - Typical antipsychotics
  - Atypical antipsychotics
- Substantial side effects
- Black box warning- cerebrovascular events and death
Antipsychotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommended Dose</th>
<th>Formulations</th>
<th>Frequency</th>
<th>Extrapyramidal Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>0.5-2.0mg</td>
<td>Tab, liquid, IM</td>
<td>Twice daily</td>
<td>Extrapyramidal symptoms</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>2.5-15mg</td>
<td>Tab</td>
<td>Daily</td>
<td>Weight gain, increased blood sugar</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>25-400mg</td>
<td>Tab</td>
<td>Three times daily (unless ER)</td>
<td>Sedating, least extrapyramidal</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>5-30mg</td>
<td>Tab, liquid, IM</td>
<td>Daily</td>
<td>Less QT</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>0.5-5mg</td>
<td>Tab, liquid, IM, IV, sub q</td>
<td>Twice daily to four times daily</td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>10-200mg</td>
<td>Tab, liquid, IV, rectal</td>
<td>Twice to three times daily</td>
<td>Very sedating</td>
</tr>
</tbody>
</table>

Black Box Warning: Not approved for use in persons with dementia for agitation and psychosis, increased risk of stroke and death

Antipsychotics and Dementia Behaviors

**Helpful**
- Agitation and aggression
- Psychosis
  - Delusions
  - Hallucinations
- Depression?

**Not Helpful**
- Day/night reversal
- Calling out
- Repetitive behaviors
- Wandering
- Apathy
- Resistive to care

Meta-analysis Schneider et al.

- Effect size for main outcome standardized to one SD unit:
  - Summary: -0.16 (-0.24, -0.08)
  - Aripiprazole: -0.22 (-0.36, -0.08)
  - Olanzapine: -0.11 (-0.30, -0.08)
  - Quetiapine: -0.17 (-0.34, -0.01)
  - Risperidone: -0.15 (-0.32, -0.03)

- Greater effect sizes for those without psychosis
Discontinuation of Risperidol for Agitation/Aggression and/or Psychosis

Antipsychotic Summary

- Modest efficacy for treatment of agitation in dementia
- NNT 5 to 14
- Studies usually short duration: 6-12 weeks
- Large placebo effect- 30% on average
- No difference in efficacy between typical and atypical antipsychotics
- Typical antipsychotics greater side effects
Cholinesterase Inhibitor and Neuropsychiatric symptoms

Donepezil for Agitation

Memantine and Neuropsychiatric Behaviors
Summary: DICE

• Describe the behavior
• Investigate the underlying contributors/causes
• Create intervention- Non-pharmacologic and pharmacologic
• Evaluate the interventions effectiveness

Case 1:
61 y/o with Huntington’s who presents to the IPU with impulsivity and agitation- not slept in 2 days, more confused, pacing, eating food out of garbage. Patient recently admitted to hospice with functional decline, falls, weight loss, dysphagia, and worsening behaviors. Interventions to date: Haldol 5mg every 6 hours and every 2 hours as needed, mirtazapine 30mg at night, sertraline 50mg daily, lorazepam 1mg every 6 hours and 1 hour as needed, amantadine 200mg daily. Urinalysis and bloodwork were unremarkable and patient was not in pain. Patient transferred to the IPU for further management of impulsivity and agitation.

Case 1:
• Describe: Huntington’s with impulsivity and agitation/restlessness
• Investigate: Medication regimen
• Create:
  • Discontinue amantadine, mirtazapine and sertraline
  • Decrease Haldol 1mg every 6 hours and lorazepam 0.5 every 8 hours
  • Start trazadone 50 mg morning and 100mg QHS, start citalopram 10 mg twice daily
• Evaluate 1:
  • Increase trazadone 100mg morning and 200mg QHS
  • Start dextromethorphan and quinidine
• Evaluate 2:
  • Continue current treatment and discharge home to wife
Case 2:

86 Y/O with cerebral atherosclerosis with recent functional decline and in past 2 weeks bedbound, fall, stage II sacrum, poor appetite and weight loss, and increased agitation/aggression. Daughter took patient out of ALF after hitting and trying to bite several staff. She spends most of the day yelling and swearing, kicking, and very restless in bed. Comorbidities: hard of hearing, poor vision, arthritis, peripheral vascular disease, history of stroke, hypertension, depression, and HF. Patient admitted to hospice and transferred to the IPU for management of vocalizations and agitation/aggression. Bloodwork and urinalysis were unremarkable.

Case 2:

- Describe: Agitation and aggression including hitting and biting, worse when approach or touch or move patient
- Investigate: Pain, hearing loss, and vision loss
- Create:
  - APAP 1,000mg every 6 hours, glasses, hearing aides and speak before approach, Trazadone 25mg morning and 50mg night, morphine 5mg as needed
- Evaluate 1
  - Citalopram 10mg twice daily
  - Increase trazadone 50mg morning and 100mg evening
- Evaluate 2
  - Risperidone 0.5mg twice daily

Questions?