Management of Behavioral Symptoms in Dementia

David Mansoor, MD
Geriatric Psychiatrist
Assistant Professor of Psychiatry
OHSU/PVAMC
Conflict of Interest Disclosure

• None.
Overview

• Epidemiology
• Evaluation of neuropsychiatric symptoms
  – Identify target behaviors
  – Mental status exam
• Environmental and medical causes
• Non-pharmacological interventions
• Medication management
  – Symptom oriented approach
Objectives

• Distinguish between “agitation” and “aggression” in dementia
• Identify common reversible causes
• Describe the symptom oriented approach to treating behavioral symptoms
• Develop a plan for treating these behaviors
Epidemiology

• Dementias can be categorized by possible etiology
  – Alzheimer’s dementia
  – Vascular dementia
  – Dementia with Lewy bodies
  – Frontotemporal lobar degeneration
  – Secondary dementia
    • B12 deficiency, HIV, alcohol, etc.
Epidemiology

- Loss in intellectual abilities
- Impairment in judgment
- Loss of executive function
- Personality changes
- Behavioral changes -> neuropsychiatric symptoms
Epidemiology: Neuropsychiatric Symptoms

- Common – a central component of dementia
- Morbid
- Classifiable
- Treatable
## Epidemiology: Prevalence of Symptoms in Dementia

<table>
<thead>
<tr>
<th>NPI Item</th>
<th>Dementia (n=329)</th>
<th>No Dementia (n=673)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apathy</td>
<td>27.4%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Depression</td>
<td>23.7%</td>
<td>7.0%</td>
</tr>
<tr>
<td>Agitation/aggression</td>
<td>23.7%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Irritability</td>
<td>20.4%</td>
<td>4.5%</td>
</tr>
<tr>
<td>Delusions</td>
<td>18.5%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>17.0%</td>
<td>5.6%</td>
</tr>
<tr>
<td>Aberrant motor behavior</td>
<td>14.3%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>13.7%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>9.1%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Elation</td>
<td>0.9%</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

Peak Frequency of Behavioral Symptoms as Alzheimer's Disease Progresses

Prevalence (% of patients)

Months Before/After Diagnosis

General Approach to Behavioral Complications of Dementia

- Characterize target symptoms
  - If due to medical disorder: treat and monitor behavioral symptoms
  - Medical evaluation
  - Environmental evaluation
  - Mental status exam
  - Nonpharmacological approaches
  - Treat and monitor behavioral symptoms: drug therapy
Target Symptoms

• Before any intervention is initiated, observation and documentation to measure the nature, severity, and frequency of the symptoms

• Details are critical for directing care

• Selection of an intervention depends on the targeted behavioral symptom
Target Symptoms: Case

• You’re on call and receive a page from a care facility,
  – Your patient is an 82-year old patient with advanced Alzheimer’s disease who has been at an adult foster home for 2 years
  – “He is having problems. We need something to calm him down.”
    • “he is agitated”
Target Symptoms: Case

- Define target behaviors
- A precise description can assist with identifying the underlying cause and selection of effective interventions
- “Agitation” is commonly used
  - It is nonspecific
  - It is not a diagnostic term
  - No universal definition
  - Often subjectively assigned by an observer depending on whether or not the behavior seems appropriate
  - It’s cause is frequently multifactorial
Target Symptoms: Case

• Agitation includes
  – General restlessness
  – Pacing
  – Complaining
  – Repeating sentences
  – Cursing
  – Kicking
  – Hitting
  – Name calling
Target Symptoms: Case

• Aggressive
  – Physical
  – Verbal

• Nonaggressive
  – Physical
  – Verbal
Target Symptoms: Case

• Physical aggression: hostile acts directed toward others, self, or objects
  – Hitting, kicking, biting, grabbing, scratching
  – Tend to occur in later stages
  – Often during times of close contact
  – More common in men than women
  – More common in those with premorbid aggression
Target Symptoms: Case

- Verbal aggression: temper outbursts, making strange noises, screaming, cursing, threatening, accusations, name calling
Target Symptoms: Case

• Physical nonaggression: repetitive activities
  – Wandering, pacing, checking, disrobing, repeating
gestures or movements

• Verbal nonaggression: complaining, repeating
words and sentences, constant talk, calling out
Target Symptoms: Case

• At a clinic visit, a caregiver says your patient Mrs Y is having “hallucinations”
• She is a 75-year old with moderate Alzheimer’s disease who lives at home
Target Symptoms: Case

• Define the target behavior / symptom
• Delusions?
  – Paranoid?
    • Spouse having an affair; stealing; others in the house
  – Misidentifiﬁcation?
• Hallucinations?
  – Auditory?
  – Visual?
General Approach to Behavioral Complications of Dementia

- If due to medical disorder: treat and monitor behavioral symptoms
- Characterize target symptoms
- Medical evaluation
- Environmental evaluation
- Mental status exam
- Nonpharmacological approaches
- Treat and monitor behavioral symptoms: drug therapy
Evaluation - Environment

• Environment
  – Overstimulating?
    • TV, telephone, visitors, mirrors, pictures...
  – Understimulating?
    • Dark, quiet, reduced sensory input
  – Unfamiliar
Evaluation – Medical

- Pain
  - Musculoskeletal
  - Constipation
  - Urinary retention
  - Hunger, thirst
- Infection
- Medications
  - Benzodiazepines, opiates, anticholinergics
Evaluation – Medical

• Basic labs as indicated
  – CBC, chemistry panel, TSH
  – B12 if it hasn’t been done
  – Urinalysis

• Imaging only as indicated
  – New neurologic finding
  – Recent fall with head injury
Evaluation – Mental Status Exam

• General appearance:
  – Grooming? Weight? In pain?
  – Attention?

• Speech:
  – Spontaneous? Fluent?

• Affect:
  – Anxious? Depressed?

• Thought process
  – Disorganized? Linear?
Evaluation – Mental Status Exam

• Though content:
  – Delusional? Hallucinations? Empty?

• Cognition:
  – 30-pt mental status exam
    • How far off from baseline?
    • tests of attention can help to distinguish delirium from dementia
Evaluation: Case

• 78 year old with Parkinson’s disease dementia referred for “agitation”
  – History: moved to new care facility; tries to get up out of wheelchair and falls; strikes out at caregivers when they try to prevent him from falling
  – MSE: cooperative, bradykinetic, minimal speech; caregiver reports VH
Evaluation: Case

• Why is he getting up?
  – Environment?
  – Pain? Toilet?

• Intervention
  – Keep him occupied
  – Walk him frequently
  – Approach slowly -> inquire about needs
General Approach to Behavioral Complications of Dementia

- Characterize target symptoms
  - If due to medical disorder: treat and monitor behavioral symptoms
- Medical evaluation
- Environmental evaluation
- Mental status exam
- Nonpharmacological approaches
- Treat and monitor behavioral symptoms: drug therapy
Non-Pharmacological Approach

• Develop a structured daily routine
• Offer daytime recreational therapy
• Increase physical activity during the day and avoid napping
• Create a quiet and comfortable sleep environment
• Limit evening fluid intake, empty bladder
• Bright light during the day and darkness at night
• Avoid caffeine, alcohol, nicotine
Non-pharmacological Approach

• Bathing: make bathroom safe, comfortable room and water temp, don’t rush, wash hair last, towel bath
• Dressing: limit choices, prepare clothing, large clothing and soft stretchy fabric, Velcro shoes
• Eating: maintain regular mealtime, avoid distraction, check food temperature, finger foods, sweeten foods,
Non-pharmacological Approach

• Wandering: provide adequate daily physical activity, create safe wandering paths, remove reminders of leaving (coats, umbrellas), alarms or bells at door exits, ID bracelet
• Incontinence: schedule voiding, nonverbal cues (pacing), put signs at the bathroom door, clear obstacles
• Delusions: avoid challenging
Non-pharmacological Approach

- Music therapy
- Bright light therapy
- Aromatherapy
- Pet therapy
General Approach to Behavioral Complications of Dementia

- characterize target symptoms
- medical evaluation
- environmental evaluation
- mental status exam
- nonpharmacological approaches
- treat and monitor behavioral symptoms:
  - drug therapy

if due to medical disorder:
- treat and monitor behavioral symptoms
Considerations

• There are no FDA approved medications for treating behavioral symptoms due to dementia
• There is no magic bullet
• Often multi-factorial etiology
Considerations

• When using a medication, do so judiciously, in the lowest effective doses, and for the shortest period of time necessary
  – Start low and go slow (but go!)

• Age related physiologic change -> more susceptible to side effects
Considerations

• Ineffective medications should be stopped
• Consideration should be given to periodic trial dose reductions of effective medications to learn whether treatment is still necessary
Behaviors Resistant to Medications

- Calling out/repetition/vocalizations
- Wandering/exit-seeking
- Disrobing
- Hoarding
- Inappropriate voiding
SYMPTOM ORIENTED APPROACH
Symptom Oriented Approach

Traditional Approach

- Signs and Symptoms

New Approach

- Symptom
  - Treat (e.g., “psychosis”)

Potential Diagnoses
- AD
- DLB
- TBI
- Vascular

Diagnosis
- Treat (e.g., “pneumonia”)
Symptom Oriented Approach to Treatment

- Define the target behaviors
- Look for a pattern in the patient's behavior which is analogous to that typically seen in a "drug responsive" psychiatric syndrome

- Psychotic – overly suspicious, angry when approached, delusional
- Depressive – irritable, sad, vegetative, withdrawn
- Manic – euphoric, accelerated, hypersexual, labile affect
- Anxious – worry, restless, somatic concerns
Symptom Oriented Approach to Treatment

- Match the target symptom to the drug class

<table>
<thead>
<tr>
<th>Behavioral disturbance</th>
<th>Drug to consider</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressive Spectrum</td>
<td>Antidepressant</td>
</tr>
<tr>
<td>Psychotic Spectrum</td>
<td>Antipsychotic, CI</td>
</tr>
<tr>
<td>Manic</td>
<td>Mood Stabilizer</td>
</tr>
<tr>
<td>Anxiety Spectrum</td>
<td>SSRI</td>
</tr>
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Symptom Oriented Approach to Treatment

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<tr>
<td>Aggression / Anger Mild / Acute</td>
<td>Trazodone</td>
</tr>
<tr>
<td>Aggression / Anger Mild / Longterm</td>
<td>SSRI, Trazodone, Depakote, Cl</td>
</tr>
<tr>
<td>Aggression / Anger Severe Acute</td>
<td>Antipsychotic</td>
</tr>
</tbody>
</table>
TREATMENT BY DRUG CLASS

“Each capsule contains your medication, plus a treatment for each of its side effects.”
Considerations

• Multiple classes of psychotropic medication have demonstrated efficacy in treating agitation
  – Antidepressants
  – Mood stabilizers
  – Cholinesterase inhibitors
  – Antipsychotics
Antidepressants
(for Depression and Agitation)
Antidepressants - Agitation

• Few studies of antidepressants for the treatment of agitation and psychosis in dementia
• Most studies have been small, did not control for depressive symptoms, varying results
Antidepressants - Agitation

• Cochrane Review 2011:
  – The SSRIs sertraline and citalopram were associated with a reduction in symptoms of agitation when compared to placebo in two studies
  – Both SSRIs and trazodone appear to be tolerated reasonably well when compared to placebo, typical antipsychotics and atypical antipsychotic

• “Antidepressants such as citalopram, sertraline, and trazodone may improve symptoms of agitation and psychosis for some individuals with dementia and given that the tolerability and safety of these medications appears to be similar to placebo and certain antipsychotics, these medications may be considered as a potential treatment for these symptoms”
Antidepressants - Agitation

• APA Practice Guidelines (2007)
  – “a therapeutic trial of trazodone, buspirone, or an SSRI may be appropriate for some nonpsychotic but agitated patients, especially those with relatively mild symptoms or those who are intolerant of or unresponsive to antipsychotics”
Antidepressants – Agitation

• Consider for agitation driven by a mood disorder
• Avoid older tricyclics (Amitriptyline, Imipramine, etc)
• Start low and go slow
  – Citalopram
  – Sertraline
  – Mirtazapine
  – Trazodone PRN or scheduled
# Antidepressants - Agitation

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<tr>
<th>DRUG</th>
<th>STARTING DOSE</th>
<th>TITRATION</th>
</tr>
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<tbody>
<tr>
<td>citalopram</td>
<td>10mg</td>
<td>up to 20mg after 6 weeks</td>
</tr>
<tr>
<td>sertraline</td>
<td>25-50mg</td>
<td>up to 25-50mg increments every 6 weeks</td>
</tr>
<tr>
<td>fluoxetine</td>
<td>10mg</td>
<td>up to 40mg in 10 mg increments every 6 weeks</td>
</tr>
<tr>
<td>mirtazapine</td>
<td>7.5mg</td>
<td>up to 45mg in 7.5mg increments every 6 weeks</td>
</tr>
<tr>
<td>trazodone</td>
<td>12.5-25mg bid PRN or scheduled</td>
<td>25mg qday increments up to about 150mg</td>
</tr>
</tbody>
</table>
Antidepressants - Depression

• APA Practice Guidelines (2007)
  – “Although evidence for antidepressant efficacy in patients with dementia and depression is mixed, clinical consensus supports a trial of an antidepressant to treat clinically significant, persistent depressed mood. The choice among agents is based on the side-effect profile of specific medications and the characteristics of the individual patient. SSRIs may be preferred because they appear to be better tolerated than other antidepressants. Bupropion, venlafaxine, and mirtazapine may also be effective.”

• American Academy of Neurology - “SSRIs should be considered to treat depression”
## Antidepressants - Depression

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<tr>
<td>mirtazapine</td>
<td>7.5mg</td>
<td>up to 45mg in 7.5mg increments every 6 weeks</td>
</tr>
<tr>
<td>venlafaxine xr</td>
<td>37.5mg</td>
<td>up to 225mg in 37.5mg increments</td>
</tr>
</tbody>
</table>
Antidepressants – Side Effects

- Constipation
- Diarrhea
- Dizziness
- Dry mouth
- Falls
- Nervousness
- Headache

- Nausea
- Tremor
- Decreased libido
- Gait instability
- Fatigue

Cognitive Enhancers: Cholinesterase Inhibitors and Memantine
Cholinesterase Inhibitors

- Increase Ach in the synaptic cleft
- Galantamine, Rivastigmine, Donepezil
  - 2009 Systematic Review: mixed
  - Generally well tolerated, benefit cognition and function, worth trying if symptoms are mild or if risks of other medications are high
  - Dementia with Lewy bodies
  - Frontotemporal dementia

## Cholinesterase Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting dose</th>
<th>Titration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aricept (donepezil)</td>
<td>5mg qhs</td>
<td>10mg qhs after one month</td>
</tr>
<tr>
<td>Razadyne (galantamine)</td>
<td>4mg bid</td>
<td>4mg bid q month up to 12mg bid; dose renally</td>
</tr>
<tr>
<td>Exelon (rivastigmine)</td>
<td>1.5mg bid</td>
<td>1.5mg q 2 weeks up to 6mg bid; dose renally</td>
</tr>
</tbody>
</table>
Cholinesterase Inhibitors

• Adverse effects
  – Bradycardia
  – AV Block
  – Syncope
  – Seizures
  – Peptic ulcer
  – Hallucinations
  – Nausea
  – Vomiting
  – Diarrhea
  – Abdominal pain
  – Confusion
  – Sedation

• Drug interactions
  – Anticholinergics
  – Bupropion
  – Beta blockers
  – NSAIDs
Memantine

- Memantine (Namenda)
  - Binds NMDA receptor, inhibits influx of Ca$^{2+}$ ions, reduces glutamate induced neuronal toxicity
  - Indicated for moderate to severe Alzheimer’s
  - Literature is also mixed and limited
    - Most studies recruited patients for the purpose of testing cognition, not behavioral symptoms
  - Also generally well tolerated, with cognitive and functional benefit in patients with moderate to severe dementia
Memantine

• Start 5mg qday, increase in 5mg increments every week up to 10mg bid
• Dose renally, 5mg po bid for CrCl 5-29
• Adverse reactions: dizziness, confusion, somnolence, vomiting, hallucinations, constipation
• Drug interactions: few
Mood Stabilizers
Valproic Acid

- Anecdotal reports abound along with positive open label studies
- Effective in a broad range of psychiatric conditions characterized by agitation
- Consider for aggressive / impulsive behavior in the absence of psychotic symptoms or mood lability
- Valproate, Cochrane 2009 review
  - “...Valproate preparations are ineffective in treating agitation among demented patients, and that Valproate therapy is associated with an unacceptable rate of adverse effects” (falls, GI, sedation)
  - Limited by 3 small studies of poor quality

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting Dose</th>
<th>Titration</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depakote</td>
<td>125mg bid</td>
<td>125-250mg increments up to about 1000mg in 24 hours, divided doses</td>
<td>Sedation, GI upset, tremor, thrombocytopenia</td>
</tr>
</tbody>
</table>
Antipsychotics
Antipsychotics

• Traditional mainstay for reducing agitation for decades
• May increase mortality and stroke
• Benefits often still outweigh the risks in patients when treatment of hallucinations and delusions are critical
  – Individual risk/benefit analysis
Antipsychotics

• Less-severe behaviors with limited consequences of harm to individual or caregiver ➔ non-pharmacologic therapy, not antipsychotic therapy

• More severe or “high risk” behaviors such as frightening hallucinations, delusions or hitting ➔ consider addition of antipsychotic trial
Antipsychotics

• Typical Antipsychotics, Haloperidol
  – Cochrane Review updated in 2010
    • Haloperidol was useful in the control of aggression/hostility/suspiciousness
    • “There is little evidence to support a benefit of haloperidol on manifestations of agitation other than aggression”
    • Adverse effects more common than placebo

• Atypical Antipsychotics
  – 2006 Cochrane Review of placebo-controlled trials
    • Risperidone 1-2mg and olanzapine 5-10mg improved aggression compared to placebo
    • Risperidone improved psychosis relative to placebo
# Antipsychotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting dose</th>
<th>titration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine</td>
<td>2.5 to 5mg</td>
<td>2.5mg every 2 to 3 days, to 10 mg or therapeutic effect</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>12.5-25mg</td>
<td>12.5mg every 2 to 3 days to 150mg or therapeutic effect</td>
</tr>
<tr>
<td>Risperidone</td>
<td>.25mg bid</td>
<td>.25mg every 2 to 3 days to 3mg or therapeutic effect</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>.25 bid</td>
<td>.25mg bid up to about 1mg bid</td>
</tr>
</tbody>
</table>
Antipsychotics

• Side effects: EPS, orthostasis, akathisia, sedation, metabolic, cerebrovascular events, upper respiratory tract infection, cardiac events

• Cumulative incidence of tardive dyskinesia 26%, 52%, and 60% after 1, 2, and 3 years\(^1\)
  – Typical neuroleptics

Other: Benzodiazepines and Diphenhydramine
Benzodiazepines and Diphenhydramine

• Benzodiazepines
  – Minimal data supporting efficacy
  – Sedation, falls, cognitive impairment
  – Should be avoided

• Diphenhydramine
  – Anticholinergic
  – Avoid
Hypnotics for Sleep
Hypnotics

- Try to implement non-pharm interventions
- Consider a trial of trazodone
- Consider a trial of mirtazapine if there are coexisting mood or anxiety symptoms
- Melatonin – literature is mixed
  - Studies have looked at doses 2mg-10mg
  - Generally well tolerated
- Do no use antipsychotics solely as hypnotics
Summary
“Pearls”

• Use data to formulate a hypothesis of cause of behavior

• Start with nonpharmacological approaches

• Reserve pharmacotherapy for behaviors that are severe, persistent, and/or resistant to nonpharmacological treatments
“Pearls”

• If monotherapy fails, use judicious combination of medications (eg, antidepressants with antipsychotics or with mood stabilizers)
“Pearls”

• If lots of medications do not help, start discontinuing medications
  – Can they be any worse off medications?
  – Are they experiencing interactive side effects?
“Pearls”

- Less-severe behaviors with limited consequences of harm to individual or caregiver are appropriate for nonpharmacologic therapy, not antipsychotic therapy
- More severe or “high risk” behaviors such as frightening hallucinations, delusions or hitting may require addition of antipsychotic trial