Management of Behavioral Symptoms in Alzheimer’s Dementia

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Conflict of Interest Disclosure

• None.
Overview

• Epidemiology
• Evaluation of neuropsychiatric symptoms
  – Identify target behaviors
  – Distinguish “agitation” from “aggression”
  – Mental status exam
• Environmental and medical causes
• Non-pharmacological interventions
• Medication management
  – Symptom oriented approach
Epidemiology

• Dementias can be categorized by possible etiology
  – Alzheimer’s dementia
  – Vascular dementia
  – Dementia with Lewy bodies
  – Frontotemporal lobar degeneration
  – Traumatic brain injury
  – Substance induced
  – Parkinson’s disease
  – Etc.
Epidemiology

• Nomenclature using DSM 5
  – “Dementia” replaced with “major neurocognitive disorder”
    • Prompted to specify the etiology
      – Major NCD due to Alzheimer’s disease
      – Major NCD with Lewy Bodies
      – Major vascular NCD
      – Major frontotemporal NCD

• I will be using the terms “dementia” and “neurocognitive disorder” interchangeably
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
  - Affect up to 80% of persons with dementia
- Morbid
  - Greater impairments in IADLs, more rapid rate of cognitive decline, earlier institutional decline, greater rate of caregiver depression
- 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)

- Agitation
- Irritability
- Wandering
- Aggression
- Hallucinations
- Socially unacc.
- Delusions
- Sexually inappr.
- Social withdrawal
- Depression
- Paranoia
- Suicidal ideation
- Anxiety
- Mood change
- Accusatory
- Paranoia
- Suicidal ideation
- Depression

Months Before/After Diagnosis

OHSU
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 are 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 sundowning. 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
  – Often associated with discomfort
Target Symptoms: Case

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

• Aggressive
  – Physical
  – Verbal

• Nonaggressive
  – Physical
  – Verbal
Target Symptoms

• 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
Target Symptoms

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

• 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

- Helps to understand etiology
  - Wandering: looking for home? bathroom? anxiety? akathisia?
  - Aggression: psychosis? fear? pain?
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
- Hallucinations?
  - Auditory?
  - Visual?
- Delusions?
  - Paranoid?
    - Spouse having an affair; stealing; others in the house
  - Misidentification? (Capgras delusion)
General Approach to Behavioral Complications of Dementia

- Characterize target symptoms
  - Medical evaluation
  - Environmental evaluation
  - Mental status exam
  - Nonpharmacological approaches

If due to medical disorder: treat and monitor behavioral symptoms

Treat and monitor behavioral symptoms: drug therapy
Evaluation: Mental Status Exam

- General appearance:
  - Grooming? Weight? In pain? Level of consciousness?
- Behavior
- Speech
  - Quantity? Smooth/effortless or halting?
- Language
  - Word finding difficulty → General use-phrases (“that thing,” “you know what I mean”) with comprehension difficulty
- Mood
  - “How are your spirits today?”
- Affect
  - Anxious? Depressed?
Evaluation: Mental Status Exam

• Thought process
  – Linear? Circumlocution? Disorganized?

• Thought content
  – Delusional? Hallucinations?

• Insight
  – Anosognosia

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

• Discomfort / Pain
  – Musculoskeletal
  – Constipation
  – Urinary retention
  – Hunger, thirst

• Infection

• Medications
  – Benzodiazepines, opiates, anticholinergics, antihistamines
Evaluation – Medical

• Basic labs as indicated
  – CBC, chemistry panel, TSH, b12
  – Urinalysis for urinary tract symptoms

• Imaging only as indicated
  – New neurologic finding
  – Recent fall with mental status change, headache, neurologic findings
Evaluation - Environment

• Environment
  – Overstimulating?
    • TV, telephone, visitors, mirrors, pictures...
  – Understimulating?
    • Dark, quiet, reduced sensory input
  – Unfamiliar
    • Transition can be disruptive
General Approach to Behavioral Complications of Dementia

- Characterize target symptoms
- Medical evaluation
- Environmental evaluation
- Mental status exam
- Nonpharmacological approaches

If due to medical disorder: treat and monitor behavioral symptoms.
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
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
Considerations

• There are no FDA approved medications for treating behavioral symptoms due to dementia
• There is no magic bullet
• Typically need a combination of behavioral intervention and pharmacotherapy
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
SYMPTOM ORIENTED APPROACH
Symptom Oriented Approach

Traditional Approach  New Approach

Signs and Symptoms

Symptom

Treat (e.g., “psychosis”)

AD  DLB  TBI  Vascular

Potential Diagnoses

Treat

Diagnosis (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 – impulsive, 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</td>
</tr>
<tr>
<td>Manic</td>
<td>Mood Stabilizer</td>
</tr>
<tr>
<td>Anxiety Spectrum</td>
<td>SSRI</td>
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</table>
Symptom Oriented Approach to Treatment

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<tr>
<th>Behavioral disturbance</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Aggression / Anger Mild / Acute</td>
<td>Trazodone</td>
</tr>
<tr>
<td>Aggression / Anger Mild / Longterm</td>
<td>SSRI, Depakote, CI</td>
</tr>
<tr>
<td>Aggression / Anger Severe / Acute</td>
<td>Antipsychotic</td>
</tr>
</tbody>
</table>
“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

• Often used because well tolerated and have few serious side effects

• 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 - 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

• Consider for depression or agitation driven by underlying depression
• Avoid older tricyclics (amitriptyline, imipramine, etc)
• Start low and go slow
  – Escitalopram
  – Sertraline
  – Mirtazapine
  – Trazodone PRN or scheduled
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 \(^1\)
  - 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 \(^2\)

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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
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
- Sedation, GI upset, tremor, thrombocytopenia

Antipsychotics
Antipsychotics

• Traditional mainstay for reducing agitation for decades

• May increase mortality and stroke
  – 1.6 x increase in mortality compared with placebo (4.5% vs 2.6%)

• Benefits often still outweigh the risks in patients when treatment of hallucinations and delusions are critical
  – Individual risk/benefit analysis
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

- 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
- Avoid in dementia with Lewy bodies!!!

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Other: Benzodiazepines and Diphenhydramine
Benzodiazepines and Diphenhydramine

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

• Diphenhydramine
  – Anticholinergic
  – Avoid
  – May worsen cognition and behaviors
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
• Do not use hydroxyzine, Benadryl, or benzos!
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.
Question

You are treating a patient with very distressing paranoia due to advanced Alzheimer’s disease. This has led to caregiver mistrust, refusal of care, and physically aggressive behavior. You plan to start an antipsychotic medication. In discussing the risks and benefits of antipsychotics in older adults with behavioral symptoms associated with dementia, which of the following is accurate:

A. A black box warning exists because of the increased risk of death
B. Antipsychotic medications can help to treat parkinsonism symptoms, if present
C. Antipsychotic medications slow progression of cognitive decline in patients with Alzheimer’s disease
D. Antipsychotics lower the risk of stroke
Question

• You are consulting on a 72-year old woman who suffers from dementia with Lewy bodies. She has distressing visual hallucinations and has been acting on the delusion that people are in the room trying to harm her. Which of the following medications should be avoided because of the risk of worsening parkinsonism:

A. Haloperidol (first generation anti-psychotic)
B. Donepezil (cholinesterase inhibitor)
C. Trazodone (anti-depressant)
D. Memantine (NMDA receptor antagonist)
Question

• Your patient is an 82-year old woman with moderate stage Alzheimer’s disease. For the past 3 weeks she has been suspicious of her caregivers and having difficulty sleeping. Which of the following medications are FDA approved for treating behavioral symptoms in Alzheimer’s disease:

   A. Antipsychotics
   B. Antidepressants
   C. Cholinesterase inhibitors
   D. No medications are FDA approved for treating behavioral symptoms in Alzheimer’s disease
Question

• Your patient is an 80-year old with moderate Alzheimer’s disease. He presents with symptoms of apathy and low motivation. Neuropsychiatric symptoms are seen in approximately what percentage of patients with dementia:
  A. 0-10%
  B. 10-20%
  C. 30-50%
  D. 60-80%
Question

• You are evaluating a 75-year old patient with early Alzheimer’s disease. He describes a several month history of low mood and sleep disturbance. Which of the following symptoms would support a diagnosis of major depression:
  A. Visual hallucinations
  B. Skin picking
  C. Decreased appetite with weight loss
  D. Disorientation
The End

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