Behavioral and Pharmacologic Approaches to Agitation Associated with Major Neurocognitive Disorders

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Faculty Disclosure

• Marc E. Agronin, MD has no financial relationships to disclose relating to the subject matter of this presentation.
Disclosure

• The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).
  – There is no universally recognized or FDA-designated indication for agitation in dementia; all medications discussed in this presentation for the treatment of agitation in dementia is off-label.

• Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.

• This activity has been independently reviewed for balance.
Learning Objectives

- Describe the common manifestations of agitation and psychosis associated with major neurocognitive disorders
- Assess the individual demonstrating agitation and/or psychosis and determine potential causes
- Apply both behavioral and pharmacologic strategies to reduce the frequency and intensity of agitation and psychosis
Case Report

- Mrs. Rose is an 87-year-old woman living in a condo with her husband
- She has chronic pain and mild cognitive impairment
- Her daughter calls you to report:
  - She is crying and screaming a lot
  - She is fighting with her husband
  - She is accusing her husband of having an affair
  - She gets so agitated at times that she throws herself on the ground and her husband has to call 911 to get her up

### ISSUES
- Pain
- Confusion
- Sadness / grief
- Paranoia
- Marital discord
- Deconditioning
- Sedating medications
- Inadequate help

### DIAGNOSIS
- What is causing her problematic behaviors?
- How do we measure and monitor her behaviors?

### TREATMENT
- What is the least restrictive way to improve her behaviors?
- When are medications needed?
What is Agitation?

*and where does it come from?
What is Agitation?

According to the International Psychogeriatric Association, Agitation involves

- Excessive motor activity, or verbal or physical aggression, that
- Causes observed (or inferred) emotional distress, and
- Is “severe enough to produce excess disability,” and
- Significant impairment in
  - Interpersonal relationships,
  - Social functioning, and/or
  - The ability to perform or participate in daily living activities

The Range of Behavioral Disturbances

• PHYSICAL AGITATION
  – Aggression / assaultiveness
  – Destructiveness
  – Grabbing / groping
  – Self-injurious behaviors (eg, hitting self)

• VOCAL / VERBAL AGITATION
  – Screaming / cursing
  – Repetitive vocalizations

• OTHER
  – Intrusive wandering
  – Elopement from a safe area
  – Resistance to necessary care
  – Hoarding or hiding objects
  – Disinhibition (eg, disrobing; inappropriate comments)
**Agitation is one of many**

Behavioral and Psychological Symptoms of Dementia

<table>
<thead>
<tr>
<th>Depression</th>
<th>Mania</th>
<th>Anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apathy</td>
<td><strong>Agitation</strong></td>
<td>Psychosis</td>
</tr>
</tbody>
</table>

Wandering – Excessive Motor Activity – Intrusiveness

Resistance – Disinhibition – Sleep Disturbances

The Burden of Agitation

- It is estimated that 80% to 90% of patients with neurocognitive disorders demonstrate various forms of BPSD, with some of the highest rates observed in more severe dementia and in nursing home populations.

- Agitation is associated with:
  - Accelerated disease progression
  - Disproportionate reductions in function and well-being
  - Increased caregiver stress
  - Increased costs of caregiving
  - Increased risk of long-term care placement
  - Increased mortality

BPSD = behavioral and psychological symptoms of dementia.

What Causes Agitation?
A Vulnerable Brain: Neurocircuitry

Neurocognitive disorders create a brain more vulnerable to agitation due to structural damage to key neurocircuits or networks and their functions

- **Affective Regulation**: Our ability to perceive and interpret both emotionally laden events and potential threats can be disrupted, leading to inappropriate and agitated emotional responses

- **Executive Function**: Our ability to understand, organize, prioritize, and respond to challenges and problems can be disrupted, leading to disorganized, exaggerated, and dysfunctional behaviors

A Vulnerable Brain: Neurochemistry (cont’d)

Neurocognitive disorders create a brain more vulnerable to agitation due to metabolic changes in key neurotransmitter systems

• **Cholinergic** deficits in the nucleus basalis, hippocampus, and frontotemporal regions are associated with cognitive impairment, agitation, and aggression

• **Serotonergic** deficits are associated with depression, agitation, aggression, and impulse dyscontrol, especially with cell loss in the raphe nucleus

• **Dopaminergic** deficits may render individuals more sensitive to developing spontaneous and drug-induced movement disorders

Key Triggers / Causes of Agitation

- Medical Conditions
- Psychiatric Conditions
- Medications
- Psychological Factors
- Environmental Factors

Medical and Psychiatric Causes

**Medical / Neurologic**
- Neurocognitive disorders
- Delirium
- Pain
- Infection
- Metabolic disturbances (eg, hyponatremia)

**Psychiatric**
- Depression
- Anxiety
- Panic attacks
- Phobias
- Psychosis
- Substance use
- Sleep disturbances
- Intellectual disability
- Personality disorders
Psychotic Symptoms

**Delusions**
- Paranoid
  - Items are being stolen
  - Caregiver wants to harm person
  - Spouse is having an affair
- Misidentification
  - House is not one’s own
  - Spouse is someone strange
  - Someone strange in the mirror
- Somatic
  - Persistent, unusual symptom
  - Parasitic infestation

**Hallucinations**
- Visual
  - Seeing people (large or small)
  - Seeing insects or animals
- Auditory
  - Voices
  - Noises
  - Music
- Olfactory and tactile are less common and typically have specific medical causes (e.g., seizures; substance withdrawal)
# How Do Neurocognitive Disorders Shape Agitation?

<table>
<thead>
<tr>
<th>Dementia</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s Disease</td>
<td>Agitation is common in middle and later stages of disease</td>
</tr>
<tr>
<td>Vascular Dementia</td>
<td>Frontal and temporal lesions can cause disinhibition Subcortical damage associated with apathy</td>
</tr>
<tr>
<td>Dementia with Lewy Bodies</td>
<td>Fluctuating confusion / delirium and psychosis often triggers agitation</td>
</tr>
<tr>
<td>Frontotemporal Dementia</td>
<td>Associated with prominent personality changes, bizarre behaviors, disinhibition, compulsions, and hypersexuality</td>
</tr>
<tr>
<td>Parkinson’s Disease</td>
<td>Paranoid delusions and/or visual hallucinations due to disease and/or dopaminergic agents can trigger agitation</td>
</tr>
<tr>
<td>Traumatic Brain Injury</td>
<td>Often associated with disinhibition and impulsivity due to frontal lobe damage</td>
</tr>
</tbody>
</table>
Medications and Substances

- Anticholinergics (eg, scopolamine)
- Antibiotics (eg, quinolones)
- Pain medications
  - Opioid narcotics (morphine, hydrocodone, etc.)
  - Muscle relaxants (carisoprodol, cyclobenzaprine)
- Steroids
- Dopaminergic agents (eg, levodopa)
- Stimulants (eg, methylphenidate)
- Substances (eg, cocaine, alcohol)
Psychological Factors

- Fears
- Grief
- Unmet needs (e.g., hunger, thirst)
- Exhaustion
- Boredom
- Overstimulation
- Poor insight and judgement
Environmental Causes

• Inappropriate Caregiving
  – Abuse, neglect, lack of training
• Inappropriate Setting
  – Lack of structure or routine, too confining, lack of stimulation, annoying or uncomfortable ambience, excessive social or functional demands
• Impaired Caregiver
  – Depressed, nervous, incompetent, burnt out, exhausted, medically or psychiatrically ill

How Do We Assess Agitation?
Challenges to Assessment

- Behavioral disturbances are often intermittent and unpredictable
- Patients often cannot provide accurate history
- Reports may be variable, inaccurate, and subject to interpretation – depending on the expertise and observation schedule of the informant
Basic Questions

BEHAVIORS
• What behaviors are being seen?
• How often? How severe?
• Are they new or recurrent behaviors?
• What was the patient’s baseline?
• Is there risk of harm to self or others?

TRIGGERS
• Any consistent causal events?
• Is the trigger an underlying condition or interaction?

CONSEQUENCES
• What happens as a result of the behavior?
Relevant Workup

- **Labs**: Urinalysis, complete blood count, electrolytes, calcium, hepatic and renal function, thyroid function
- **Imaging**: Chest X-ray if infection suspected; brain CT or MRI if there are acute mental status or functional changes, neurologic symptoms or significant personality change
- **Physical / Neurological Exam**: Look for sources of pain and infection
- **Mental Status Exam**: Look for changes from baseline

CT = computed tomography; MRI = magnetic resonance imaging.
Applied Behavior Analysis

• Dementia reduces a person’s repertoire of behaviors, and a person’s attempts to adapt in more limited ways may be disruptive

• The ABA model helps us to better understand these behaviors by examining the CONTEXT in which they occur and their FUNCTION

• Thus – in-depth assessment of the behavior is critical, and involves interviews of individual and caregivers and observation of behaviors

• 5 main functions of behavior (PASTE)
  – Pain attenuation
  – Attention
  – Stimulation
  – Tangibles (eg, food)
  – Escape

• The function of the behavior will guide the treatment approach

ABA = applied behavior analysis.
ABA Model of Behavioral Management

- **Antecedent Stimuli**: Environmental or internal conditions that trigger the problem behavior
- **Behavior**: Actions that are observable and measurable, i.e., operationalized (e.g., *Mr. Jones hitting the nurse with his fist during breakfast*)
- **Consequences**: What occurs immediately after the problem behavior and serves to increase, decrease, or maintain the current level of behavior
- **Motivational Variables**: Make the consequences more or less valuable (e.g., social isolation increases the value of attention)

Mrs. Rose is an 87-year-old woman living in a condo with her husband. She has chronic pain and mild cognitive impairment.

<table>
<thead>
<tr>
<th>Antecedents</th>
<th>Behaviors</th>
<th>Consequences</th>
<th>Motivation</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caregivers leave house</td>
<td>Crying</td>
<td>Caregivers return → crying stops</td>
<td>Social isolation</td>
<td>ATTENTION</td>
</tr>
<tr>
<td>Physical pain; hunger</td>
<td>Screaming</td>
<td>Pain meds given; food given → pain improves</td>
<td>Lifelong history of med seeking and overeating</td>
<td>TANGIBLES</td>
</tr>
<tr>
<td>Incontinence that requires changing</td>
<td>Fighting</td>
<td>Caregiver tries to change quickly → increases screaming</td>
<td>Very sensitive skin makes any contact uncomfortable</td>
<td>PAIN ATTENUATION / ESCAPE</td>
</tr>
<tr>
<td>Female caregiver chats with husband</td>
<td>Accusations of affair</td>
<td>Husband denies it to wife and massages back → calms her</td>
<td>Insecure attachment to husband</td>
<td>ATTENTION / STIMULATION</td>
</tr>
</tbody>
</table>
How Do We Treat Agitation?
Basic Treatment Algorithm

- **Safety**: Ensure safety if there is potential for injury to self or others
- **Causes**: Treat identifiable and reversible physical causes
- **Behavioral Approaches**: In the moment and over time
- **Pharmacologic Approaches**: Start low, go slow, but go
- **Re-evaluation**: Is it working? Are more modalities needed? What was missed?
## The DICE Algorithm

<table>
<thead>
<tr>
<th>Domain</th>
<th>Elements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Describe</td>
<td>Obtain description of behaviors from caregivers</td>
</tr>
<tr>
<td></td>
<td>Review the context of the behaviors (when, where, with whom)</td>
</tr>
<tr>
<td>Investigate</td>
<td>Examine patient factors (eg, medical and psychiatric conditions, and medications), caregiver factors, environmental factors, and cultural factors</td>
</tr>
<tr>
<td>Create</td>
<td>Team approach to respond to physical problems, develop behavioral approaches, and devise pharmacologic approach</td>
</tr>
<tr>
<td>Evaluate</td>
<td>Evaluate the degree of implementation of the plan and the overall results</td>
</tr>
</tbody>
</table>
Safety

• The risk of NOT treating or UNDERtreating can be risky
• Delirium poses the most danger due to acute injury, persistent medical issues, and subacute cognitive decline
• Injury to self or others must be addressed right away, and this will help to prioritize approaches (eg, more rapid use of medications)
• For acute danger, involuntary ER assessment and inpatient psychiatric hospitalization must be considered

ER = emergency room.
Causes

- Meet unmet needs in the moment (eg, food, hydration) and in the long run (eg, impaired or incompetent caregiver)
- Treat underlying medical and/or psychiatric conditions
- Simplify and optimize medication regimen by eliminating PIPs
- Re-evaluate on a regular basis since there is often not a single quick fix

PIP = potentially inappropriate prescription.
Potentially Inappropriate Prescription

PIPs can occur when medications are given under the following circumstances

• No clear evidence-based indication
• Higher dose or longer time than necessary
• Combined with medication from same class
• Combined with a drug with known drug-drug interactions
• Given with high risk for drug-disease interaction
• Given after incorrect diagnosis
• Not adjusted for hepatic, renal, cardiac, or other changes
• Withheld or given due to ageism or prejudice, or for punitive reasons
• Continued despite lack of efficacy or ongoing side effects
• Given without non-drug strategies

Basic Behavioral Approaches

• Empathic acknowledgement with active listening
• Address unmet needs (e.g., hunger, thirst) and environmental irritants (e.g., excessive noise, heat or cold, disruptive roommates)
• Focus on abilities instead of deficits
• Engage family and other familial caregivers
• Know the person well in terms of interests, preferences, habits
• Distract and re-direct
• **It takes a village**: Informal and professional caregivers and specialists
• Involve in stimulating, pleasant activities
• Use individualized behavioral interventions (e.g., ABA Model)

### Therapeutic Activities

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory intervention</td>
<td>Music, massage, white noise, sensory stimulation</td>
</tr>
<tr>
<td>Social contact</td>
<td>One-to-one, pets, simulated presence, and videos</td>
</tr>
<tr>
<td>Behavior therapy</td>
<td>Differential reinforcement, stimulus control</td>
</tr>
<tr>
<td>Staff training</td>
<td>In-services on communication, empathy, etc.</td>
</tr>
<tr>
<td>Structured activities</td>
<td>Group activities, outdoor walks, exercise groups</td>
</tr>
<tr>
<td>Environmental</td>
<td>Wander areas, reduced noise, natural sounds/sights</td>
</tr>
<tr>
<td>Medical/nursing</td>
<td>Pain control, hearing aides, restraint removal</td>
</tr>
<tr>
<td>Combination</td>
<td>Combining modalities (eg, behavioral + medications)</td>
</tr>
</tbody>
</table>

# Therapeutic Activities: Research Findings

<table>
<thead>
<tr>
<th>Study</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Literature review and meta-analysis of 179 RCTs of therapeutic activities across 26 intervention categories</td>
<td>Good evidence to support improvement in neuropsychiatric symptoms using multicomponent interventions, such as group activities, music, and physical exercise</td>
</tr>
<tr>
<td>Literature review and meta-analysis of 317 RCTs highlighting 7 types of interventions</td>
<td>Sensory interventions showed statistically significant differences in agitation between interventions and control groups for aromatherapy, thermal bath, calming music, and hand massage</td>
</tr>
</tbody>
</table>

RCT = randomized controlled trial.
ABA Model: Behavioral Intervention

• The overall goal is to prevent the behavior rather than simply react to it
• The basic strategy is to
  – Understand the function of the behavior within a specific context (eg, a patient gets agitated to escape the discomfort during dressing changes)
  – Change the environment so the individual gets their needs met another way, OR
  – Substitute the disruptive behavior for a more adaptive one
• This can be accomplished by either
  – Modifying the antecedents or consequences, OR
  – Differentially reinforcing other more adaptive behaviors

Case Report: *Treatment Plan*

Mrs. Rose is an 87-year-old woman living in a condo with her husband. She has chronic pain and mild cognitive impairment.

<table>
<thead>
<tr>
<th>Antecedents</th>
<th>Behaviors</th>
<th>Consequences</th>
<th>Motivation</th>
<th>Function</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caregivers leave house</td>
<td>Crying</td>
<td>Caregivers return</td>
<td>Social isolation</td>
<td>ATTENTION</td>
<td>Day Program with music and groups</td>
</tr>
<tr>
<td>Physical pain; hunger</td>
<td>Screaming</td>
<td>Pain or food improves pain</td>
<td>Med seeking / overeating</td>
<td>TANGIBLES</td>
<td>Reduce antecedents with more regular pain meds and snacks</td>
</tr>
<tr>
<td>Incontinence that requires changing</td>
<td>Fighting</td>
<td>Quick changes increase screaming</td>
<td>Very sensitive skin makes any contact uncomfortable</td>
<td>PAIN ATTENUATION / ESCAPE</td>
<td>Change consequence by slowing down changes and providing soothing balm</td>
</tr>
<tr>
<td>Female caregiver chats with husband</td>
<td>Accuses husband of affair</td>
<td>Husband denial and massage calms her</td>
<td>Insecure attachment to husband</td>
<td>ATTENTION / STIMULATION</td>
<td>Reinforce patient’s request for attention that isn’t paranoid</td>
</tr>
</tbody>
</table>
How Do We Treat Agitation Using Medications?
When Are Medications Needed?

- Dangerous or severe symptoms
- Behavioral approaches are not working
- Underlying psychiatric disorder (e.g., bipolar disorder)
- Psychotic symptoms
Pharmacologic Treatment Dilemmas

• There is no universally recognized or FDA-designated indication for agitation in dementia
• All psychotropic medication use is thus “off-label”
• Efficacy is limited and variable, with high placebo effects
• There are several important potential side effects

Pharmacologic Treatment: Basic Rules

- Older individuals may be more sensitive to medications
- Be aware of comorbid medical conditions
- Try to avoid drug-drug interactions
- Watch for oversedation, dizziness, and blood pressure changes
- Start low, go slow (50% of adult dose), but Go
- Keep in mind OBRA, Beers Criteria, and other relevant guidelines in long-term care settings

# Psychotropics Used for Agitation

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotics</td>
<td>Best efficacy in studies, although benefits are modest and variable; works for psychosis</td>
<td>Metabolic side effects EPS / Movement disorders Increased mortality</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Works quickly and effectively for calming and sedation Versatile; as-needed dosing</td>
<td>Excess sedation and fall risk Increased confusion Paradoxical effects</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Addresses serotonergic function Treats underlying depression and anxiety</td>
<td>Takes time to work (ie, weeks) Can sometimes increase agitation Side effects not always tolerated</td>
</tr>
<tr>
<td>Mood Stabilizers</td>
<td>Best for underlying mania, bipolar disorder, or recurrent depression</td>
<td>Poor efficacy in studies Metabolic effects Serum levels required</td>
</tr>
<tr>
<td>Cholinergic Agents</td>
<td>Used to boost cognition May reduce incidence of agitation</td>
<td>Poor efficacy, especially in acute situations</td>
</tr>
<tr>
<td>Others</td>
<td>dextromethorphan + quinidine; prazosin; β-blockers; estrogen</td>
<td></td>
</tr>
</tbody>
</table>

EPS = extrapyramidal symptoms.
Reasons to Use Antipsychotics

- Schizophrenia and other chronic psychotic disorders
- Bipolar disorder
- Augmentation for major depression

- Delirium
- Dementia with psychosis
- Dementia with agitation

= FDA Indication  = NO FDA Indication
The Controversy over Antipsychotics

• They are often used and there is data supporting their use
• In 2010, Senator Grassley requested that the OIG evaluate the use of antipsychotics in nursing homes due to concerns about off-label use
• According to the OIG report from May 2011
  – Despite the boxed warning about increased mortality, 83% of Medicare claims were for off-label indications, and 88% of residents using them had dementia
  – The implication is that there is a problem—despite the lack of any FDA-approved condition or alternative medications
• Nonpharmacologic approaches recommended as first-line treatment for dementia-related behaviors

OIG = Office of Inspector General.
Antipsychotic Medications in Dementia

Most commonly used
- Haloperidol
- Risperidone
- Olanzapine
- Quetiapine
- Aripiprazole
## Clinical Trials: Atypical Antipsychotics in Dementia

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Trial</th>
<th>N</th>
<th>Mean Age</th>
<th>Duration (weeks)</th>
<th>Efficacy vs Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>Katz et al</td>
<td>625</td>
<td>83</td>
<td>12</td>
<td>Improved symptoms</td>
</tr>
<tr>
<td></td>
<td>De Deyn et al</td>
<td>344</td>
<td>81*</td>
<td>12</td>
<td>Improved symptoms</td>
</tr>
<tr>
<td></td>
<td>Brodaty et al</td>
<td>337</td>
<td>83</td>
<td>12</td>
<td>Improved symptoms</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Satterlee et al</td>
<td>238</td>
<td>Not available (≥ 65)</td>
<td>8</td>
<td>No difference</td>
</tr>
<tr>
<td></td>
<td>Street et al</td>
<td>206</td>
<td>83</td>
<td>6</td>
<td>Improved symptoms</td>
</tr>
<tr>
<td></td>
<td>De Deyn et al</td>
<td>652</td>
<td>77</td>
<td>10</td>
<td>Improved symptoms (7.5 mg)</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Tariot et al</td>
<td>284</td>
<td>84</td>
<td>10</td>
<td>Improved agitation, but not psychosis</td>
</tr>
<tr>
<td></td>
<td>Zhong et al</td>
<td>333</td>
<td>83</td>
<td>10</td>
<td>Improved agitation (200 mg/day)</td>
</tr>
</tbody>
</table>

*Median age.

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Trial</th>
<th>N</th>
<th>Mean Age</th>
<th>Duration (weeks)</th>
<th>Efficacy vs Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>Streim et al</td>
<td>256</td>
<td>83</td>
<td>10 weeks</td>
<td>No difference in symptoms of PAD, clinically meaningful reduction of behavioral symptoms approaching 10 mg</td>
</tr>
<tr>
<td></td>
<td>Mintzer et al</td>
<td>487</td>
<td>83</td>
<td>10</td>
<td>Improved symptoms of PAD at 10 mg, agitation reduced at 5 and 10 mg</td>
</tr>
<tr>
<td></td>
<td>De Deyn et al</td>
<td>208</td>
<td>82</td>
<td>10</td>
<td>Inconsistent, aripiprazole 10 mg/day was effective on BPRS-psychosis vs placebo</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>None</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Lee et al</td>
<td>16</td>
<td>cases</td>
<td>cases</td>
<td>“Beneficial” in cases of treatment-resistant agitation</td>
</tr>
</tbody>
</table>

BPRS = Brief Psychiatric Rating Scale; PAD = psychotic symptoms associated with Alzheimer disease.
The CATIE – AD Trial

36-week double-blind, placebo-controlled trial of N=421 patients with AD + psychosis, aggression, or agitation treated with 1 of 3 atypical antipsychotics that looked at time to discontinuation for any reason as the main outcome. Overall, 82% stopped medication during the study.

**Table:**

<table>
<thead>
<tr>
<th></th>
<th>Olanzapine</th>
<th>Risperidone</th>
<th>Quetiapine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>100</td>
<td>85</td>
<td>94</td>
<td>142</td>
</tr>
<tr>
<td>Median Dose</td>
<td>5.3 mg</td>
<td>1.0 mg</td>
<td>56.5 mg</td>
<td>----</td>
</tr>
<tr>
<td>Time to D/C</td>
<td>22.1 months*</td>
<td>26.7 months*</td>
<td>9.1 months</td>
<td>9.0 months</td>
</tr>
<tr>
<td>Did Not Tolerate</td>
<td>24%</td>
<td>18%</td>
<td>16%</td>
<td>5%*</td>
</tr>
<tr>
<td>% Improved</td>
<td>32%</td>
<td>29%</td>
<td>26%</td>
<td>21%</td>
</tr>
</tbody>
</table>

A Review of Meta-Analyses

**Basic challenges of antipsychotics:** They are frequently used, especially in long-term care, but with limited monitoring, variable efficacy, and moderate-to-high risk of side effects

- Review of meta-analysis
  - Risperidone, olanzapine, and aripiprazole have modest benefits for aggression and psychosis in dementia
  - There is less robust evidence for quetiapine
  - Adverse events are increased, especially cerebrovascular events, sedation, abnormal gait, EPS, and death
  - Most people tolerate discontinuation, although those with higher baseline behavioral problems often have worsening symptoms

Increased Use, Increased Side Effects

Main Side Effect Concerns
- Weight gain
- Hyperglycemia
- Increased lipid levels
- Movement disorders
- Elevated prolactin levels
- Cerebrovascular events
- Increased mortality?

Obesity
Diabetes
Hyperlipidemia

Cardiovascular Disease

Atypical Antipsychotics: Mortality Warning

FDA Black Box Warning Concerning the Potential Increased Mortality in Elderly Patients with Dementia-Related Psychosis Treated with Antipsychotic Agents

- Affects elderly patients with dementia-related psychosis
- Analyses of 17 placebo-controlled trials revealed risk of death in drug-treated patients between 1.6 and 1.7× that seen in placebo-treated patients (4.5% vs 2.6%)
- Most deaths cardiovascular (eg, heart failure, sudden death) or infectious (pneumonia)
- Differences between individual antipsychotics not reported
- No study showed a statistically significant difference in mortality, but trend of increased mortality appeared in 15/17 studies

Unintended Effects

- Clinicians may switch to non-antipsychotic medications which have less efficacy and equal side effect issues.
- Clinicians may not adequately treat the symptoms because they minimize doses or use less efficacious antipsychotic medications.
- Clinicians may stop antipsychotics used for critical diagnoses, such as bipolar disorder and schizophrenia.
- Antipsychotics may be withheld or stopped due to arbitrary reasons, such as needing to reduce usage below certain percentages in order to optimize star ratings in long-term care settings.
Risk Management with Antipsychotics

- **Remember**: Off-label usage is permitted as long as there is justification in the literature or medical community.
- Documentation must justify the clinical rationale for its use and recognition that risks outweigh benefits.
- Documentation of discussion with patient and/or legally authorized representative is important.
- Follow appropriate dosing and management – including frequent re-assessment.
- Avoid inappropriate uses such as for insomnia, mild anxiety, or depression, or on a PRN basis in nursing homes.

## Antidepressants

<table>
<thead>
<tr>
<th>Drug</th>
<th>N</th>
<th>Weeks</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram vs placebo</td>
<td>98</td>
<td>16</td>
<td>AD, but not VaD patients had improved irritability</td>
</tr>
<tr>
<td>Citalopram vs perphenazine</td>
<td>85</td>
<td>2.5</td>
<td>Citalopram effect size 0.64; perphenazine 0.36</td>
</tr>
<tr>
<td>Fluvoxamine vs placebo</td>
<td>46</td>
<td>6</td>
<td>No improvement over placebo</td>
</tr>
<tr>
<td>Sertraline vs placebo</td>
<td>22</td>
<td>4</td>
<td>Sertraline with significant improvement on agitation, aggression, and irritability</td>
</tr>
<tr>
<td>Sertraline vs placebo</td>
<td>144</td>
<td>12</td>
<td>No significant difference overall</td>
</tr>
<tr>
<td>augmentation of donepezil</td>
<td></td>
<td></td>
<td>Moderate–severe group with 60% vs 40% improvement</td>
</tr>
<tr>
<td>Trazodone vs haloperidol</td>
<td>149</td>
<td>16</td>
<td>No difference between agents</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>34% improvement rate overall</td>
</tr>
</tbody>
</table>

VaD = vascular dementia.

Mood Stabilizers

<table>
<thead>
<tr>
<th>Drug</th>
<th>N</th>
<th>Weeks</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine vs placebo</td>
<td>51</td>
<td>6</td>
<td>Significant improvement</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>21</td>
<td>6</td>
<td>Significant improvement</td>
</tr>
<tr>
<td>Divalproex sodium</td>
<td>56</td>
<td>6</td>
<td>Significant improvement</td>
</tr>
<tr>
<td>Divalproex sodium vs placebo</td>
<td>42</td>
<td>3</td>
<td>No difference over placebo</td>
</tr>
<tr>
<td>Divalproex sodium vs placebo</td>
<td>153</td>
<td>6</td>
<td>No difference over placebo</td>
</tr>
<tr>
<td>Divalproex sodium vs placebo</td>
<td>14</td>
<td>6</td>
<td>Worsening agitation and aggression compared to placebo</td>
</tr>
</tbody>
</table>

# Other Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Outcome / Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Enhancers</td>
<td>No significant data aside from overall decreased frequency of behavioral disturbances in AD trials</td>
</tr>
<tr>
<td>β-blockers</td>
<td>Several small trials suggest improvement in agitation with propranolol and pindolol</td>
</tr>
<tr>
<td>Estrogen</td>
<td>No consistent findings to support efficacy over placebo</td>
</tr>
<tr>
<td>α-blocker</td>
<td>Prazosin has been found useful in reducing agitation</td>
</tr>
<tr>
<td>Trazodone</td>
<td>Excellent alternative to benzodiazepines for short-term reduction in agitation</td>
</tr>
<tr>
<td>Dextromethorphan-Quinidine</td>
<td>Modest evidence showing behavioral improvement in agitation</td>
</tr>
</tbody>
</table>

OBRA contained a series of Nursing Home Reform Amendments to improve care in nursing homes, including ways to reduce unnecessary use of psychotropic medications

- Requirement to involve mental health providers to provide adequate assessment and documentation
- There is a focus on surveillance of antipsychotics and benzodiazepines
- LTC institutions must work with pharmacies to ensure proper management
- Surveyors will review this documentation and facilities can be cited for noncompliance
- F-tag 329 looks specifically at unnecessary drug use

CMS = US Centers for Medicare & Medicaid Services; LTC = long-term care.
Unnecessary Drug Use According to F329

Drug therapy (especially antipsychotic use) is considered “unnecessary” after determining that the facility’s use of the drug involves one of the following:

- Excessive dose
- Excessive duration
- Inadequate monitoring
- Lack of indication
- Adverse consequences

Beers Criteria

The Beers Criteria for Potentially Inappropriate Medication Use in Older Adults, also called the Beers List, were first developed in 1991 by geriatrician Mark Beers, MD to improve the care of older individuals by providing a list of potentially dangerous medications. Since 2011, the American Geriatric Society have been revising and updating the list based on both consensus and evidence-based approaches.

Examples of problematic medications include:
- Anticholinergics
- Antihistamines (first-generation: diphenhydramine)
- Tricyclic antidepressants (eg, nortriptyline)
- Antipsychotics
- Benzodiazepines

# OBRA / CMS Guidelines

## Benzodiazepines

<table>
<thead>
<tr>
<th>Name</th>
<th>Maximum Recommended Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>5 mg</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>1.5 mg</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>2 mg (1 mg / sleep)</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>0.75 mg (0.25 mg / sleep)</td>
</tr>
<tr>
<td>Temazepam</td>
<td>7.5 mg (sleep)</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>5 mg (sleep)</td>
</tr>
</tbody>
</table>

## Antipsychotics

<table>
<thead>
<tr>
<th>Name</th>
<th>Maximum Recommended Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>4 mg</td>
</tr>
<tr>
<td>Risperidone</td>
<td>2 mg</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>10 mg</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>200 mg</td>
</tr>
<tr>
<td>Clozapine</td>
<td>50 mg</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>8 mg</td>
</tr>
</tbody>
</table>

How to Manage Psychotropics in Long-Term Care

• Have a psychiatrist or psychiatric ARNP conduct assessment and follow-up
• Implement and document nonpharmacologic strategies
• For each psychotropic medication prescribed, document the relevant diagnosis and the rationale for using the medication
• PRN antipsychotics not recommended except for brief tapers
• When possible, attempt gradual dose reductions or document why it is not recommended or possible (eg, chronic symptoms in schizophrenia and risk of relapse; previous relapse when taper attempted)
• Ideally, document conversations with patients and families with respect to consent and risks vs benefits
Electroconvulsive Therapy

What happens when all behavioral and pharmacologic approaches do not adequately work?

• One review looked at multiple studies using ECT for agitation and aggression in dementia, N=122 individuals
• 88% had a clinically significant response to ECT
• Side effects were mild and transitory
• More research is needed

ECT = electroconvulsive therapy.
Summary

• Agitation is ubiquitous in dementia
• Comprehensive assessment is critical to identify causes and determine the context and function of behaviors
• Behavioral approaches and interventions, both simple and complex, are the mainstay of treatment
• There are many pharmacologic options, but their efficacy is limited and variable, and side effects are common