AGITATION AND PSYCHOSIS IN DEMENTIA: PRACTICAL MANAGEMENT
Learning Objectives

• Describe the clinical presentation of psychosis and agitation in dementia

• Employ pharmacological and non-pharmacological treatment strategies to ameliorate psychosis and agitation in patients with dementia
PSYCHOSIS IN DEMENTIA

Psychosis is a possible contributor to rejection of care, leading potentially to agitation or aggression
# Prevalence of Psychosis in Dementia

<table>
<thead>
<tr>
<th>Psychosis Type</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s disease</td>
<td>25-40%</td>
</tr>
<tr>
<td>Dementia with Lewy Bodies</td>
<td>75%</td>
</tr>
<tr>
<td>Parkinson’s disease dementia</td>
<td>50-60%</td>
</tr>
<tr>
<td>Frontotemporal dementia</td>
<td>5-10%</td>
</tr>
<tr>
<td>Vascular Dementia</td>
<td>15%</td>
</tr>
</tbody>
</table>

Stahl SM, Morrissette DM. *Stahl’s Illustrated Alzheimer’s Disease and Other Dementias* 2019.
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)
Neurobiological Basis of Psychosis: 3 Theories

Dopamine theory

Glutamatergic NMDA theory

Serotonin SHT2A theory

Stahl SM, Morrissette DM. Stahl’s Illustrated Alzheimer’s Disease and Other Dementias 2019.
Neurobiological Basis of Psychosis: Dopamine Theory

Stahl SM, Morrissette DM. Stahl’s Illustrated Alzheimer's Disease and Other Dementias 2019.
Neurobiological Basis of Psychosis: Antipsychotic Treatment

Stahl SM, Morrissette DM. Stahl’s Illustrated Alzheimer’s Disease and Other Dementias 2019.
Neurobiological Basis of Psychosis: Glutamatergic NMDA Theory
Neurobiological Basis of Psychosis: Serotonin 5HT2A Theory

Stahl SM, Morrissette DM. Stahl’s Illustrated Alzheimer’s Disease and Other Dementias 2019.
# Treating Psychosis: Antipsychotics

## Dosing Recommendations for Antipsychotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>6-40 mg/day</td>
</tr>
<tr>
<td>Risperidone</td>
<td>2-8 mg/day</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>10-30 mg/day</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>300-750 mg/day</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>10-30 mg/day</td>
</tr>
<tr>
<td>Clozapine</td>
<td>350 ng/mL trough plasma level</td>
</tr>
</tbody>
</table>

**FDA Black Box Warning Concerning the Potential Increased Mortality in Elderly Patients With Dementia-Related Psychosis Treated With Antipsychotic Agents-2008**

Stahl SM, Morrissette DM. Stahl’s Illustrated Alzheimer’s Disease and Other Dementias 2019.
Treating Psychosis: Pimavanserin

- 5HT2A and 5HT2C Antagonist
- No dopamine D2 binding affinity
- Approved for treatment of psychosis in Parkinson's Disease
- Effective in ↓ visual hallucinations without ↑ motor effects
- Side effects may include peripheral edema, confusion, nausea, and potential QTc prolongation

On July 20, 2020 the FDA accepted filing for pimavanserin for the treatment of hallucinations and delusions associated with dementia-related psychosis (DRP)

Based on findings from the pivotal phase III HARMONY study

Pimavanserin reduced relapse of psychosis by 2.8 fold compared to placebo (Hazard ratio = 0.353; p=0.0023)
AGITATION IN DEMENTIA

Caveat: Psychosis is a possible contributor to agitation, but persons with dementia without psychosis can become agitated as well!
What Is Agitation?

• Hallmark features:
  • Motor restlessness
  • Irritability
  • Inappropriate or purposeless verbal and/or motor activity
  • Heightened responsivity to stimuli

• Symptoms may include:
  • Non-aggressive symptoms
    • Pacing, hand wringing, fist clenching, pressured speech
  • Aggressive symptoms
    • Screaming, cursing, breaking objects, threatening others

• Agitation does not necessarily entail aggression
  • However, aggression is often (but not always) preceded by agitation

Agitation

• Affects at least 50% of patients with AD
• First-line treatment is non-pharmacological
  • Address potential unmet needs such as pain or hunger

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

Neurobiology of Agitation

• Agitation associated with psychosis, mania, and substance use = dopamine imbalance

• Agitation associated with dementia, depression, and anxiety = GABA imbalance

Acetylcholine and Agitation

prolonged (suprphysiological) DA release

prolonged burst of action potentials

= nicotine

= Ca++

= DA

Stahl's Illustrated Violence. 2014.
Assessing Agitation

- Patient interview
- Interview with family, friends, regular outpatient care providers
- Medical history
- Psychiatric history
- Substance use history
- Social and family histories
- Mental status examination
- Rating scales
Caveat: Agitation vs. Aggression

- **Agitation** and **aggression** are two different syndromes—not everyone who is agitated becomes aggressive and not every episode of aggression is immediately preceded by agitation.
  - Agitation is excessive motor or verbal activity *without any focus or intent*.
  - Aggression is a provoked or unprovoked behavior *intended* to cause harm.

- **Reactive aggression** is often precipitated by rejection of care and may not be associated with agitation.

- Psychotic patients sometimes resist such care as bathing or medication treatment; this rejection of care is stressful for care providers, and is a common reason for institutionalization.

### Assessing Agitation: Cohen-Mansfield Agitation Inventory (CMAI)

<table>
<thead>
<tr>
<th>Physical/Agressive</th>
<th>Physical/Non-Aggressive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hitting</td>
<td>Pacing, aimless wandering</td>
</tr>
<tr>
<td>Kicking</td>
<td>Inappropriate dress/disrobing</td>
</tr>
<tr>
<td>Grabbing</td>
<td>Trying to get to a different place</td>
</tr>
<tr>
<td>Pushing</td>
<td>Intentional falling</td>
</tr>
<tr>
<td>Throwing things</td>
<td>Eating/drinking inappropriate substances</td>
</tr>
<tr>
<td>Biting</td>
<td>Handling things inappropriately</td>
</tr>
<tr>
<td>Scratching</td>
<td>Hiding things</td>
</tr>
<tr>
<td>Spitting</td>
<td>Hoarding things</td>
</tr>
<tr>
<td>Hurting self or others</td>
<td>Performing repetitive mannerisms</td>
</tr>
<tr>
<td>Destroying property</td>
<td>General restlessness</td>
</tr>
<tr>
<td>Making physical sexual advances</td>
<td></td>
</tr>
<tr>
<td>Verbal/Agressive</td>
<td>Verbal/Non-Aggressive</td>
</tr>
<tr>
<td>Screaming</td>
<td>Repetitive sentences or questions</td>
</tr>
<tr>
<td>Making verbal sexual advances</td>
<td>Strange noises</td>
</tr>
<tr>
<td>Cursing or verbal aggression</td>
<td>Complaining</td>
</tr>
<tr>
<td></td>
<td>Negativism</td>
</tr>
<tr>
<td></td>
<td>Constant unwarranted request for attention</td>
</tr>
</tbody>
</table>
Principles of De-escalation and Environmental Safety

- Respect personal space
- Do not be provocative
- Establish verbal contact
- Be concise
- Identify wants and feelings
- Listen closely to what the patient is saying
- Agree or agree to disagree
- Set clear limits
- Offer choices and optimism
- Debrief the patient and staff

- Assure patient is physically comfortable
- Offer food and/or beverages
- Offer nicotine replacement
- Decrease external stimuli
- Minimize waiting time
- Remove potentially dangerous objects

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 redirect
• It takes a village: Informal and professional caregivers and specialists
• Involve in stimulating, pleasant activities
• Use individualized behavioral interventions (e.g., ABA Model)
• Sensory interventions include music, massage, white noise, sensory stimulation

• 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
• Older individuals may be more sensitive to medications
• Be aware of comorbid medical conditions
• Watch for oversedation, dizziness, and blood pressure changes
• Thus, non-pharmacologic approaches recommended as first-line treatment for dementia-related behaviors

# Psychotropics Used for Agitation

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidepressants</strong></td>
<td>Addresses serotonergic function and treats underlying depression/anxiety</td>
<td>Takes time for efficacy (i.e., weeks) Can sometimes increase agitation Side effects may not be tolerated</td>
</tr>
<tr>
<td><strong>Mood Stabilizers</strong></td>
<td>Best for bipolar disorder, underlying mania, or recurrent depression</td>
<td>Poor efficacy in studies Serum levels required Metabolic effects</td>
</tr>
<tr>
<td><strong>Antipsychotics</strong></td>
<td>Best efficacy in studies, although benefits are modest and variable; works for psychosis</td>
<td>Metabolic side effects EPS/Movement disorders <strong>Increased mortality</strong></td>
</tr>
<tr>
<td><strong>Cholinergic Agents</strong></td>
<td>Used to boost cognition May reduce incidence of agitation</td>
<td>Poor efficacy, especially in acute situations</td>
</tr>
<tr>
<td><strong>Benzodiazepines</strong></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><strong>Cholinergic Agents</strong></td>
<td>Used to boost cognition May reduce incidence of agitation</td>
<td>Poor efficacy, especially in acute situations</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td>Dextromethorphan + quinidine; prazosin; β-blockers; estrogen</td>
<td></td>
</tr>
</tbody>
</table>

EPS= extrapyramidal symptoms

### Which is best for the treatment of agitation in dementia?
Treating Agitation/Aggression

Review of Antipsychotics Used for Agitation in Dementia

<table>
<thead>
<tr>
<th>Modest Benefits for Agitation and Psychosis in Dementia</th>
<th>Improved Agitation, But Not Psychosis</th>
<th>Adverse Effects (EPS, Cerebrovascular, Sedation, Gait, Death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone (Most consistent)</td>
<td>Quetiapine</td>
<td>Risperidone</td>
</tr>
<tr>
<td>Olanzapine</td>
<td></td>
<td>Olanzapine</td>
</tr>
<tr>
<td>Aripiprazole (Inconsistent)</td>
<td></td>
<td>Aripiprazole</td>
</tr>
<tr>
<td>Clozapine (Beneficial in cases of treatment-resistant agitation)</td>
<td>Quetiapine</td>
<td></td>
</tr>
</tbody>
</table>

FDA Black Box Warning Concerning the Potential Increased Mortality in Elderly Patients With Dementia-Related Psychosis Treated With Antipsychotic Agents-2008

## Antidepressants for Agitation in Dementia

<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 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 34% improvement rate overall</td>
</tr>
</tbody>
</table>

VaD = vascular dementia. AD=Alzheimer’s Disease

## Mood Stabilizers for Agitation in Dementia

<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>153</td>
<td>6</td>
<td>No difference over placebo</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>14</td>
<td>6</td>
<td>Worsening agitation and aggression compared to placebo</td>
</tr>
</tbody>
</table>

# Other Agents for Agitation in Dementia

<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 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>

Dextromethorphan (DXM) for Agitation/Aggression

- Sigma-1 and mu opiate receptor agonist
- NMDA and nicotinic α3β4 antagonist
- SERT and NET inhibitor
- To avoid rapid metabolism:
  - Combine with CYP 2D6 inhibitor
    - Quinidine
    - Bupropion
    - Deuteration
- In the ADVANCE-1 Phase 2/3 study, DXM significantly improved Alzheimer’s disease agitation (p=0.010)
- Demonstrated rapid and substantial improvement in Alzheimer’s disease agitation starting at week 2 with statistical significance at week 3 compared to placebo
- A second pivotal trial is planned

Brexpiprazole for Agitation/Aggression

• Dopamine D2 receptor partial agonist
• Dopamine 3, serotonin 5HT1A, 5HT2A, and adrenergic alpha-1 binding properties
• Shown to significantly reduce disturbing/aggressive behavior in patients with schizophrenia
• Currently being tested for agitation in AD

## Drugs Currently in Development for Agitation in Dementia

### Table 1. Investigational drugs for agitation in dementia reviewed in this article.

<table>
<thead>
<tr>
<th>Family</th>
<th>Compound</th>
<th>Phase</th>
<th>Main pharmacological action</th>
<th>Main medication uses</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical antipsychotics</td>
<td>Aripiprazole</td>
<td>III</td>
<td>D2R partial agonist</td>
<td>Schizophrenia, BD</td>
<td>[26–31]</td>
</tr>
<tr>
<td></td>
<td>Brexpiprazole</td>
<td>III</td>
<td>D2R partial agonist</td>
<td>Schizophrenia, BD</td>
<td>[32–36]</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Citalopram</td>
<td>III</td>
<td>SSRI</td>
<td>MDD</td>
<td>[37–41]</td>
</tr>
<tr>
<td>Morphinan derivatives</td>
<td>AVP-786</td>
<td>III</td>
<td>NMDA antagonist(^b)</td>
<td>New compound</td>
<td>[42]</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>Nabilone</td>
<td>II–III</td>
<td>CBR agonist</td>
<td>Antiemetic, analgesic</td>
<td>[43–45]</td>
</tr>
<tr>
<td></td>
<td>Delta-THC</td>
<td>II</td>
<td>CBR agonist</td>
<td>Antispasmodic</td>
<td>[45–50]</td>
</tr>
<tr>
<td>Adrenergic agents</td>
<td>ORM-12741</td>
<td>II</td>
<td>α2c-adrenoceptor antagonist</td>
<td>New compound</td>
<td>[51,52]</td>
</tr>
<tr>
<td>Inositol isomers</td>
<td>ELND005</td>
<td>II</td>
<td>Aβ aggregation inhibitor</td>
<td>New compound</td>
<td>[53–57]</td>
</tr>
<tr>
<td>Serotonergic agents</td>
<td>Eltoprazine</td>
<td>II</td>
<td>5-HT1AR/1BR agonist</td>
<td>Developmental compound</td>
<td>[58–60]</td>
</tr>
</tbody>
</table>

BD, bipolar disorder; CBR, cannabinoid receptor; Delta-THC, delta-9-tetrahydrocannabinol; MDD, major depressive disorder; SS inhibitor. \(^a\) Plus quinidine. \(^b\) It also acts at α-receptors and the serotonin and norepinephrine transporters (see text).
Summary

• Psychosis and agitation are both prevalent in dementia

• To avoid escalation into aggressive and violent behaviors, better assessment of agitation in patients with dementia is needed

• Effective pharmacological treatments are available and in development to treat psychosis and agitation
Posttest Question 1

The prevalence of psychosis in frontotemporal dementia is _____?

1. 1–3%
2. 60–70%
3. 10–15%
4. 35–30%
Posttest Question 2

According to the Cohen-Mansfield Agitation Inventory (CMAI), which of the following are examples of physical/non-aggressive behaviors that indicate agitation?

1. Hitting
2. Intentional falling
3. Screaming
4. Spitting
Posttest Question 3

Dextromethorphan, which may decrease agitation in patients with Alzheimer’s disease when combined with quinidine, is a ________.

1. SERT inhibitor
2. NERT inhibitor
3. Sigma-1 and mu opiate receptor agonist
4. All of the above