Psych Congress

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

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

Cummings J, et al. *Int Psychogeriatr*. 2015;27(1):7-17.

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

DEPRESSION **MANIA** **ANXIETY**

APATHY **AGITATION** **PSYCHOSIS**

Wandering – Excessive Motor Activity – Intrusiveness

Resistance – Disinhibition – Sleep Disturbances

Lyketsos CG, et al. *Alzheimers Dement*. 2011;7(5):532-539.

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.

Selbaek G, et al. *Int Psychogeriatr*. 2014;26(1):81-91. Murman DL, et al. *Neurology*. 2002;59(11):1721-1729. Herrmann N, et al. *Can J Psychiatry*. 2015;60(4):189-199. Okura T, et al. *J Am Geriatr Soc*. 2011;59(3):473-481. Van Den Wijngaart MA, et al. *Aging Ment Health*. 2007;11(6):626-636.

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

Porsteinsson AP, et al. *Expert Opin Pharmacother*. 2017;18(6):611-620. Algase DL, et al. Need-driven dementia-compromised behavior: An alternative view of disruptive behavior. *American Journal of Alzheimer's Disease & Other Dementias*. 1996;11(6). Hall GR, et al. *Arch Psychiatr Nurs*. 1987;1(6):399-406.

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

Sultzer DL, et al. *J Neuropsychiatry Clin Neurosci*. 1995;7(4):476-484. Tekin S, et al. *Ann Neurol*. 2001;49(3):355-361. McLoughlin DM, et al. *Am J Psychiatry*. 1994;151(11):1701-1703. Sukonick DL, et al. *Arch Neurol*. 2001;58(9):1425-1428.

Key Triggers / Causes of Agitation

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

Morgan RO, et al. *Gerontologist*. 2013;53(5):738-747. Kunik ME, et al. *J Clin Psychiatry*. 2010;71(9):1145-1152.

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 (eg, seizures; substance withdrawal)

How Do Neurocognitive Disorders Shape Agitation?

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

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)

Kotlyar M, et al. In: Agronin ME, et al (Eds). *Principles and Practice of Geriatric Psychiatry*. Second Edition. Philadelphia, PA: Lippincott, Williams & Wilkins; 2011:721-733.

Psychological Factors

- Fears
- Grief
- Unmet needs (eg, 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

Kunik ME, et al. *J Clin Psychiatry*. 2010;71(9):1145-1152.

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)
  - **P**ain attenuation
  - **A**ttention
  - **S**timulation
  - **T**angibles (eg, food)
  - **E**scape
- The function of the behavior will guide the treatment approach

ABA = applied behavior analysis.

LeBlanc LA, et al. Behavioral gerontology. In: Fisher WW, et al (Eds). *Handbook of Applied Behavior Analysis*. New York, NY: Guilford Press; 2011:472-486.

ABA Model of Behavioral Management

A → B → C

---------- M ----------

- **Antecedent Stimuli**: Environmental or internal conditions that trigger the problem behavior
- **Behavior**: Actions that are observable and measurable, ie, operationalized (eg, *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 (eg, social isolation increases the value of attention)

Baker JC, et al. *J Appl Behav Anal*. 2006;39(4):469-474.

Case Report: *Revisited*

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

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

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

Domain	Elements
***D*escribe**	Obtain description of behaviors from caregivers Review the context of the behaviors (when, where, with whom)
***I*nvestigate**	Examine patient factors (eg, medical and psychiatric conditions, and medications), caregiver factors, environmental factors, and cultural factors
***C*reate**	Team approach to respond to physical problems, develop behavioral approaches, and devise pharmacologic approach
***E*valuate**	Evaluate the degree of implementation of the plan and the overall results

Kales HC, et al. *J Am Geriatr Soc*. 2014;62(4):762-769.

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.

Inouye SK, et al. *Lancet*. 2014;383(9920):911-922. Pandharipande PP, et al. *N Engl J Med*. 2013;369(14):1306-1316.

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

Desai A, et al. *Psychiatric Consultation in Long-Term Care: A Guide for Healthcare Professionals*. Second Edition. Cambridge University Press; 2017.

Basic Behavioral Approaches

- Empathic acknowledgement with active listening
- Address unmet needs (eg, hunger, thirst) and environmental irritants (eg, 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 (eg, ABA Model)

Cohen-Mansfield J, et al. *J Gerontol A Biol Sci Med Sci*. 2007;62(8):908-916.

Therapeutic Activities

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

Cohen-Mansfield J. *Curr Treat Options Neurol*. 2013;15(6):765-785.

Therapeutic Activities: Research Findings

Study	Findings
Literature review and meta-analysis of 215 intervention studies (1998–2008)	Limited moderate-to-high quality evidence for **sensory-focused strategies, aromatherapy, preferred or live music, and multisensory stimulation**
Literature review and meta-analysis of 179 RCTs of therapeutic activities across 26 intervention categories	Good evidence to support improvement in neuropsychiatric symptoms using multicomponent interventions, such as **group activities, music, and physical exercise**
Literature review and meta-analysis of 317 RCTs highlighting 7 types of interventions	Sensory interventions showed statistically significant differences in agitation between interventions and control groups for **aromatherapy, thermal bath, calming music, and hand massage**

RCT = randomized controlled trial.

Kverno KS, et al. *Int Psychogeriatr*. 2009;21(5):825-843. Olazarán J, et al. *Dement Geriatr Cogn Disord*. 2010;30(2):161-178. Kong EH, et al. *Aging Ment Health*. 2009;13(4):512-520.

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

Baker JC, et al. *J Appl Behav Anal*. 2006;39(4):469-474. Feliciano L, et al. *Clin Gerontol*. 2009;32(3):239-259.

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.

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

How Do We Treat Agitation Using Medications?

When Are Medications Needed?

Dangerous or severe symptoms

Behavioral approaches are not working

Underlying psychiatric disorder (eg, 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

Kindermann SS, et al. *Drugs Aging*. 2002;19(4):257-276. Ballard C, et al. *Cochrane Database Syst Rev*. 2006;(1):CD003476.

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

OBRA = Omnibus Budget Reconciliation Act of 1987.

Psychotropics Used for Agitation

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

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.

Office of the Inspector General; Department of Health and Human Services. May 2011. OEI-07-08-00150. Office of the Inspector General; Department of Health and Human Services. July 2012. OEI-07-08-00151.

Antipsychotic Medications in Dementia

Most commonly used

- Haloperidol
- Risperidone
- Olanzapine
- Quetiapine
- Aripiprazole

Clinical Trials: Atypical Antipsychotics in Dementia

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

***Median age.**

Katz IR, et al. *J Clin Psychiatry*. 1999;60(2):107-115. De Deyn PP, et al. *Neurology*. 1999;53(5):946-955. Brodaty H, et al. *J Clin Psychiatry*. 2003;64(2):134-143. Street JS, et al. *Arch Gen Psychiatry*. 2000;57(10):968-976. De Deyn PP, et al. *Int J Geriatr Psychiatry*. 2004;19(2):115-126. Tariot PN, et al. *Am J Geriatr Psychiatry*. 2006;14(9):767-776. Zhong KX, et al. *Curr Alzheimer Res*. 2007;4(1):81-93.

Clinical Trials: Atypical Antipsychotics in Dementia (cont'd)

Antipsychotic	Trial	N	Mean Age	Duration (weeks)	Efficacy vs Placebo
Aripiprazole	Streim et al	256	83	10 weeks	No difference in symptoms of PAD Clinically meaningful reduction of behavioral symptoms approaching 10 mg
	Mintzer et al	487	83	10	Improved symptoms of PAD at 10 mg Agitation reduced at 5 and 10 mg
	De Deyn et al	208	82	10	Inconsistent Aripiprazole 10 mg/day was effective on BPRS-psychosis vs placebo
Ziprasidone	None	-	-	-	-
Clozapine	Lee et al	16	cases	cases	"Beneficial" in cases of treatment-resistant agitation

BPRS = Brief Psychiatric Rating Scale; PAD = psychotic symptoms associated with Alzheimer disease.

Streim JE, et al. *Am J Geriatr Psychiatry*. 2008;16(7):537-550. Mintzer JE, et al. *Am J Geriatr Psychiatry*. 2007;15(11):918-931. De Deyn P, et al. *J Clin Psychopharmacol*. 2005;25(5):463-467. Lee HB, et al. *J Geriatr Psychiatry Neurol*. 2007;20(3):178-182.

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.

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

CATIE-AD = Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease; D/C = discontinuation.

Schneider LS, et al. *N Engl J Med*. 2006;355(15):1525-1538. Sultzer DL, et al. *Am J Psychiatry*. 2008;165(7):844-854.

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*

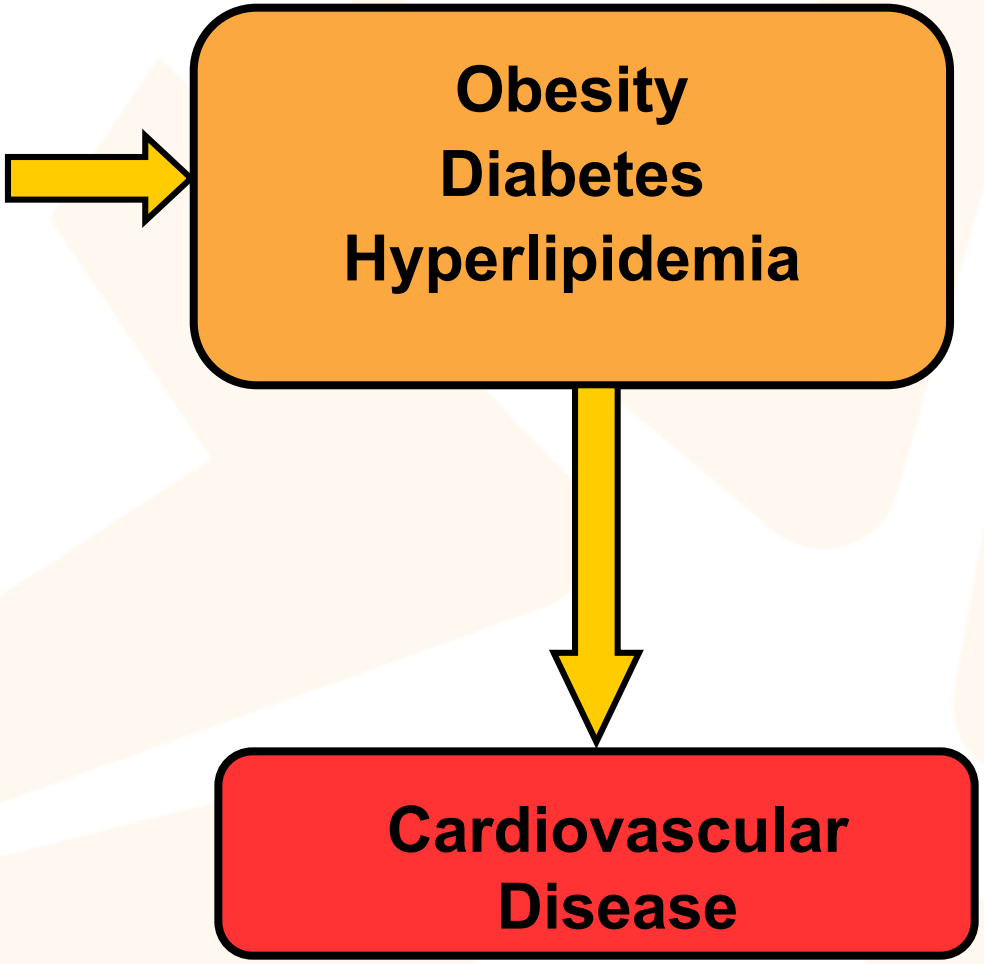
- Review of meta-analysis
  - Risperidone, olanzapine, and aripiprazole have modest benefits for aggression and psychosis in dementia
  - There is less robust evidence for quetiapine
  - Adverse events are increased, especially cerebrovascular events, sedation, abnormal gait, EPS, and death
  - Most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

Tampi RR, et al. *Ther Adv Chronic Dis*. 2016;7(5):229-245.

Increased Use, Increased Side Effects

Main Side Effect Concerns

- Weight gain
- Hyperglycemia
- Increased lipid levels
- Movement disorders
- Elevated prolactin levels
- Cerebrovascular events
- Increased mortality?



Polcwiartek C, et al. *Expert Opin Drug Saf*. 2016;15(5):679-688. Orsolini L, et al. *Expert Opin Drug Saf*. 2016;15(10):1329-1347.

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

Kuehn BM. *JAMA*. 2005;293(20):2462. *Med Lett Drugs Ther*. 2005;47(1214):61-62.

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

Reus VI, et al. *Am J Psychiatry*. 2016;173(5):543-546.

Antidepressants

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

VaD = vascular dementia.

Nyth AL, et al. *Br J Psychiatry*. 1990;157:894-901. Pollock BG, et al. *Am J Psychiatry*. 2002;159(3):460-465. Olafsson K, et al. *Acta Psychiatr Scand*. 1992;85(6):453-456. Lanctôt KL, et al. *Int J Geriatr Psychiatry*. 2002;17(6):531-541. Finkel SI, et al. *Int J Geriatr Psychiatry*. 2004;19(1):9-18. Teri L, et al. *Neurology*. 2000;55(9):1271-1278.

Mood Stabilizers

Drug	N	Weeks	Outcome
Carbamazepine vs placebo	51	6	Significant improvement
Carbamazepine	21	6	Significant improvement
Divalproex sodium	56	6	Significant improvement
Divalproex sodium vs placebo	42	3	No difference over placebo
Divalproex sodium vs placebo	153	6	No difference over placebo
Divalproex sodium vs placebo	14	6	Worsening agitation and aggression compared to placebo

Tariot PN, et al. *Am J Psychiatry*. 1998;155(1):54-61. Olin JT, et al. *Am J Geriatr Psychiatry*. 2001;9(4):400-405. Porsteinsson AP, et al. *Am J Geriatr Psychiatry*. 2001;9(1):58-66. Sival RC, et al. *Int J Geriatr Psychiatry*. 2002;17(6):579-585. Tariot PN, et al. *Am J Geriatr Psychiatry*. 2005;13(11):942-949. Herrmann N, et al. *Dement Geriatr Cogn Disord*. 2007;23(2):116-119.

Other Agents

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

Howard RJ, et al. *N Engl J Med*. 2007;357(14):1382-1392. Greendyke RM, et al. *J Nerv Ment Dis*. 1986;174(5):290-294. Peskind ER, et al. *Alzheimer Dis Assoc Disord*. 2005;19(1):23-28. Kyomen HH, et al. *Am J Psychiatry*. 2002;159(7):1225-1227. Hall KA, et al. *Int Psychogeriatr*. 2005;17(2):165-178. Cummings JL, et al. *JAMA*. 2015;314(12):1242-1254. Wang LY, et al. *Am J Geriatr Psychiatry*. 2009;17(9):744-751. Seitz DP, et al. *Cochrane Database Syst Rev*. 2011;(2):CD008191.

OBRA / CMS Guidelines / F329

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.

Scheinthal S. OBRA Guidelines. In: Agronin ME, et al (Eds). *Principles and Practice of Geriatric Psychiatry*. Second Edition. Philadelphia, PA: Lippincott, Williams & Wilkins; 2011:829-837.

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

www.cms.gov/Medicare/Provider-Enrollment-and-Certification/SurveyCertificationGenInfo/Downloads/Survey-and-Cert-Letter-16-15.pdf. Accessed July 24, 2019.

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

American Geriatrics Society 2015 Beers Criteria Update Expert Panel. *J Am Geriatr Soc*. 2015;63(11):2227-2246.

OBRA / CMS Guidelines

Benzodiazepines

Name	Maximum Recommended Daily Dose
Diazepam	5 mg
Clonazepam	1.5 mg
Lorazepam	2 mg (1 mg / sleep)
Alprazolam	0.75 mg (0.25 mg / sleep)
Temazepam	7.5 mg (sleep)
Zolpidem	5 mg (sleep)

Antipsychotics

Name	Maximum Recommended Daily Dose
Haloperidol	4 mg
Risperidone	2 mg
Olanzapine	10 mg
Quetiapine	200 mg
Clozapine	50 mg
Perphenazine	8 mg

Scheinthal S. OBRA Guidelines. In: Agronin ME, et al (Eds). *Principles and Practice of Geriatric Psychiatry*. Second Edition. Philadelphia, PA: Lippincott, Williams & Wilkins; 2011:829-837.

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.

van den Berg JF, et al. *Am J Geriatr Psychiatry*. 2018;26(4):419-434.

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