Psych Congress MasterClass

Architecture of Agitation:

Pathophysiology of Agitation in Alzheimer's Disease and Emerging Treatments

In Partnership with CAREGIVER ACTION NETWORK

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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)

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Learning Objectives

1. Define and describe the full range of behaviors indicating AAD according to IPA criteria

2. Implement strategies and tools to improve the detection and diagnosis of AAD

3. Assess the MOAs, latest clinical data, and treatment implications associated with novel/investigational medications for AAD

AAD = agitation associated with dementia due to Alzheimer's Disease; IPA = International Psychogeriatric Assocation; MOA = mechanism of action.

Overview of Agitation Associated with AD

What is Agitation?

According to the IPA, the consensus definition for agitation in cognitive disorders includes four criteria:

1. The patient meets the criteria for cognitive impairment or a dementia syndrome
2. The patient exhibits **≥1 agitation behavior(s)** with emotional dress that is persistent or frequently recurrent for **≥2 weeks** or the behavior represents a dramatic change from the patient's usual behavior
3. The behaviors are **severe and associated with excess distress or produce disability beyond that due to cognitive impairment**
4. The behaviors cannot be attributed to another psychiatric disorder, medical condition, including delirium, suboptimal care conditions, or the physiological effects of a substance

Cummings J, et al. *Int Psychogeriatr*. 2015;27(1):7-17. Sano M, et al. *Int Psychogeriatr*. 2023;1-13.

Clinical Presentation of Agitation-Related Behaviors

Agitation is comprised of three domains, which include both non-aggressive and aggressive behaviors

Agitation is common and affects about 70% of patients with Alzheimer's disease

Excessive Motor Behaviors

- Pacing
- Rocking
- Gesturing
- Pointing fingers
- Restlessness
- Performing repetitive behaviors

Verbally Aggressive Behaviors

- Yelling
- Speaking in a loud voice
- Using Profanity
- Screaming
- Shouting

Physically Aggressive Behaviors

- Grabbing
- Shoving
- Pushing
- Hitting others
- Kicking
- Biting
- Throwing Objects

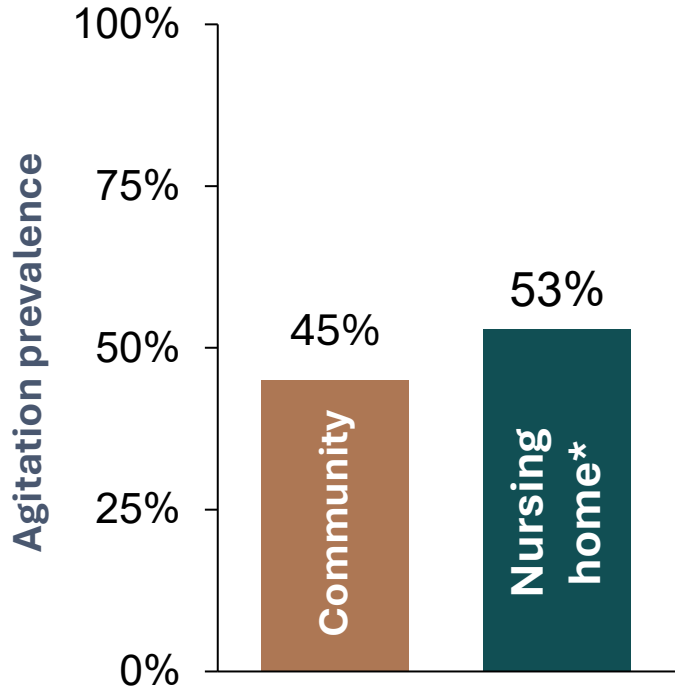
Kawas CH. *N Engl J Med*. 2003;349(11):1056–1063.

Psychotic Symptoms

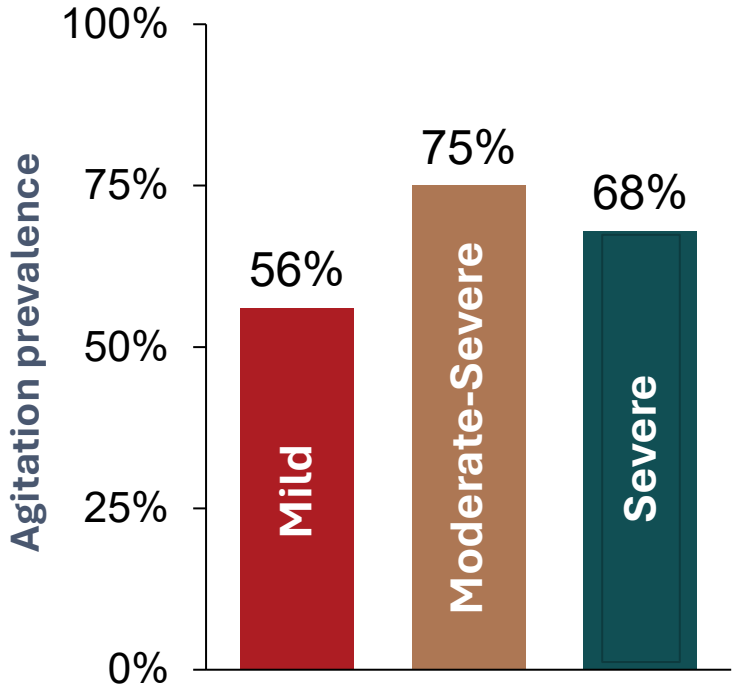
Delusions	Hallucinations
• Paranoid – Items are being stolen – Caregiver wants to harm person – Spouse is having an affair • Misidentification – House is not one's own – Spouse is someone strange – Someone strange in the mirror • Somatic – Persistent, unusual symptom – Parasitic infestation	• Visual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

AAD is Highly Prevalent Across Patient Settings and Disease Severity

Patient Care Setting



AD Severity



*Nursing home percentage reported includes patients with AD and other dementias.
AD = Alzheimer's dementia.

Kales H, et al. *BMJ*. 2015;350:h369. Halpern R, et al. *Int J Geriatr Psychiatry*. 2019;34(3):420-431. Fillit H, et al. *Int J Geriatr Psychiatry*. 2021;36(12):1959-1969.

The Burden of Agitation

Agitation has a tremendous impact on daily life and disease course

- Accelerated disease progression
- Medical events (falls, fractures, infections, 2x increased risk of hospitalizations, increased medication utilization)
- Disproportionate reductions in function and well-being
- 3.7x increased risk of long-term care placement (11.9% vs 3.2%)
- Increased mortality
- Increased caregiver stress
- Increased costs of caregiving (approximately $20,041 vs $9,243)

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; Fillit H, et al. *Int J Geriatr Psychiatry*. 2021;36(12):1959-1969. Jones E, et al. *J Alzheimer's Dis*. 2021;83(1):89-101.

Care Partners are Key

- Care partner reports and descriptions of agitation are critical to diagnosis and treatment, but may reflect both burden and bias (leading to over- or underreporting of symptoms)
- Increased severity of agitation significantly increases the time commitment and overall burden of care
- Care partners experience disproportionate increases in anxiety, depression, medical problems and even mortality

Allegri RF, et al. *Neuropsychiatr Dis Treat*. 2006;(1):105-110. Grossberg GT, et al. *Am J Geriatr Psychiatry*. 2020;28(4):383-400. Mohamed S, et al. *Am J Geriatr Psychiatry*. 2010;18(10):917-927. Okura T, et al. *Alzheimer Dis Assoc Disord*. 2011;25(2):116-121. Brodaty H, et al. *Dialogues Clin Neurosci*. 2009;11(2):217-228. Stella F, et al. *Int J Geriatr Psychiatry*. 2015;30(12):1230-1237. Amjad H, et al. *J Gen Intern Med*. 2018;33(7):1131-11387.

Key Learning Points

- International Psychogeriatric Association (IPA), the consensus definition for agitation in cognitive disorders includes four criteria
- Agitation is common and affects about 70% of patients with Alzheimer’s disease
- Agitation in Alzheimer’s Disease is highly prevalent across patient settings and disease severity
- Agitation has a tremendous impact on daily life and disease course for both patients and their caregivers

Recognition and Diagnosis of AAD

DICE: A Diagnostic and Treatment Algorithm

Domain		Elements
D	**Describe**	Obtain description of behaviors from caregivers Review the context of the behaviors (when, where, with whom)
I	**Investigate**	Examine patient factors (eg, medical and psychiatric conditions, and medications), caregiver factors, environmental factors, and cultural factors
C	**Create**	Team approach to respond to physical problems, develop behavioral approaches, and devise pharmacologic approach
E	**Evaluate**	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.

Step 1 - Assess for Safety First

- Don’t ignore acute agitation: there is great risk of potentially dangerous symptoms
- Delirium is a medical emergency and requires immediate attention and often urgent ER assessment and hospitalization
- Injury to self or others must be stopped and addressed right away, sometimes by getting the person to an ER and potentially inpatient setting
- Suicidal or homicidal threats must be addressed immediately

Step 2 – Know the Person

- Get basic demographics
- Inquire about the person’s background, history, and character
- Inquire about their habits and preferences
- Understand their most important needs and relationships
- Cultivate an empathic mindset towards them instead of a sole focus on the agitation

Step 3 – Get the Story

- **Describe the 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?
- **What are potential triggers, causes, exacerbating factors?**
  - Do any events, people, circumstances trigger agitation or make it worse?
  - Is the trigger an underlying condition, an interaction or an ambient factor?
  - What does the person seem to want when agitated?
- **What are the consequences?**
  - What happens as a result of the behavior?
  - How do people react to the agitation and how does this impact it?

Differential Diagnoses

Medical

- Infections (eg, UTI, pneumonia)
- Pain (eg, arthritis)
- Constipation
- Metabolic disturbances (eg, electrolyte imbalances, thyroid, or blood sugar)
- Neurological disorders (eg, stroke, TBI, brain tumor)
- Nutritional deficiencies (eg, B12, Thiamine)

Other Factors

- Polypharmacy (eg, benzodiazepines, opioids, anticholinergics)
- Delirium
- Depression
- Sleep Disorder (eg, untreated OSA)
- Environmental Triggers (eg, overstimulation, noise, unfamiliar setting)

American Psychiatric Association. (2022). Diagnostic and Statistical Manual of Mental Disorders (5th ed., text rev.). Differential Diagnosis section.

Challenges to Assessment

- Behavioral disturbances are often intermittent and unpredictable
- Patients often cannot provide accurate history
- Care partner, staff, and documented reports may be variable, inaccurate, and subject to interpretation—depending on the expertise and observation schedule of the informant
- Without direct observation, relevant factors can be missed
- Scales can be useful, but require time and training

Updated ICD-10 Codes

Code must include an Alzheimer's code + behavioral identifier

Alzheimer's Disease Codes

G30.0-Alzheimer's disease with early onset

G30.1-Alzheimer's disease with late onset

G30.8 Other Alzheimer's disease

G30.9 Alzheimer's disease, unspecified

Behavioral Identifier

F02.A0, B0, C0-Dementia without behaviors

F02.A1, B1, C1-Dementia with behaviors

F02.A2, B2, C2-Dementia with psychotic disturbance

F02.A3, B3, C3-Dementia with mood disturbances

F02.A4, B4, C4-Dementia with Anxiety

World Health Organization. (2024). International statistical classification of diseases and related health problems (10th rev., ICD-10). https://icd.who.int/browse10/2024/en

Early Screening and Diagnosis is Critical

- Reversible causes of cognitive impairment become less reversible with time (ie, the damage is done)
- Delays in diagnosis result in delays in treatment, research, assistance, and safeguards
- Uncertain diagnosis may lead to misdirected, inappropriate, or unsafe treatments
- It might not be dementia! This outcome can bring great relief and an appropriate search for other issues and comorbidities

$7 Trillion Dollars Saved

If every American alive today who eventually developed Alzheimer's was diagnosed at the mild cognitive impairment stage

Alzheimer's Association. 2025 Alzheimer's Disease Facts and Figures. https://www.alz.org/getmedia/ef8f48f9-ad36-48ea-87f9-b74034635c1e/alzheimers-facts-and-figures.pdf. Accessed September 15, 2025.

Available Tool for Clinical Screening and Assessment

Agitation Scales

General neuropsychiatric screening instruments

- Neuropsychiatric Inventory (NPI; structured interview and questionnaire)
- Behavioral Pathology in AD Rating Scale (BEHAVE-AD)
- Cambridge Behavioral Inventory

Assessment instruments focused on agitation

- Agitated Behavior in Dementia (ABID)
- Brief Agitation Rating Scale (BARS)
- Cohen-Mansfield Agitation Inventory (CMAI)
- Disruptive Behavior Rating Scales (DBRS)
- Pittsburgh Agitation Scale (PAS)
- Scale for Observation of Agitation in Persons With Dementia (SOAPD)

Giltin LN, et al. *Int Psychogeriatr*. 2014;26(11):1805-1848.

Cohen-Mansfield Agitation Inventory (CMAI)

- 29-item scale used to assess agitation
- Rated by a caregiver over the past two weeks
- Looks at: physical aggression, physical non-aggression, and verbal aggression
- Each item rated on a 7-point scale from never to several times per hour
- Available in several languages
- Good inter-rater reliability

Instructions: For each of the behaviors below, check the rating that indicates the average frequency of occurrence over the last 2 weeks.

Behavior	Never 1	Less Than Once a Week 2	Once or Twice a Week 3	Several Times a Week 4	Once or Twice a Day 5	Several Times a Day 6	Several Times an Hour 7
1. Hitting (including self)	❑	❑	❑	❑	❑	❑	❑
2. Kicking	❑	❑	❑	❑	❑	❑	❑
3. Grabbing onto people	❑	❑	❑	❑	❑	❑	❑
4. Pushing	❑	❑	❑	❑	❑	❑	❑
5. Throwing things	❑	❑	❑	❑	❑	❑	❑
6. Biting	❑	❑	❑	❑	❑	❑	❑
7. Scratching	❑	❑	❑	❑	❑	❑	❑
8. Spitting	❑	❑	❑	❑	❑	❑	❑
9. Hurt self or others	❑	❑	❑	❑	❑	❑	❑
10. Tearing things or destroying property	❑	❑	❑	❑	❑	❑	❑
11. Making physical sexual advances	❑	❑	❑	❑	❑	❑	❑
12. Paces, aimless wandering	❑	❑	❑	❑	❑	❑	❑
13. Inappropriate dress or disrobing	❑	❑	❑	❑	❑	❑	❑
14. Trying to get to a different place.	❑	❑	❑	❑	❑	❑	❑
15. Intentional falling	❑	❑	❑	❑	❑	❑	❑
16. Eating/drinking inappropriate substances	❑	❑	❑	❑	❑	❑	❑
17. Handling things inappropriately	❑	❑	❑	❑	❑	❑	❑
18. Hiding things	❑	❑	❑	❑	❑	❑	❑
19. Hoarding things	❑	❑	❑	❑	❑	❑	❑
20. Performing repetitious mannerisms	❑	❑	❑	❑	❑	❑	❑
21. General restlessness	❑	❑	❑	❑	❑	❑	❑
22. Screaming	❑	❑	❑	❑	❑	❑	❑
23. Making verbal sexual advances	❑	❑	❑	❑	❑	❑	❑
24. Cursing or verbal aggression	❑	❑	❑	❑	❑	❑	❑
25. Repetitive sentences or questions	❑	❑	❑	❑	❑	❑	❑
26. Strange noises (weird laughter or crying)	❑	❑	❑	❑	❑	❑	❑
27. Complaining	❑	❑	❑	❑	❑	❑	❑
28. Negativism	❑	❑	❑	❑	❑	❑	❑
29. Constant unwarranted request for attention or help	❑	❑	❑	❑	❑	❑	❑

Meunier J, et al. *Front Neurol*. 2024;15:1379062.

Neuropsychiatric Inventory (NPI)

12-item scale used to assess agitation/behaviors

Looks at different aspects of behavior and asks if it is present (Yes/No)

If present, must rate severity (mild/moderate/severe) and distress level (0-5-None at all to Extreme/Very severe)

Please answer each question honestly and carefully. Ask for assistance if you are not sure how to answer any question.

Delusions	Yes No	Does the patient believe that others are stealing from him or her, or planning to harm him or her in some way? Severity: 1 2 3 Distress: 0 1 2 3 4 5
Hallucinations	Yes No	Does the patient act as if he or she hears voices? Does he or she talk to people who are not there? Severity: 1 2 3 Distress: 0 1 2 3 4 5
Agitation or aggression	Yes No	Is the patient stubborn and resistive to help from others? Severity: 1 2 3 Distress: 0 1 2 3 4 5
Depression or dysphoria	Yes No	Does the patient act as if he or she is sad or in low spirits? Does he or she cry? Severity: 1 2 3 Distress: 0 1 2 3 4 5
Anxiety	Yes No	Does the patient become upset when separated from you? Does he or she have any other signs of nervousness, such as shortness of breath, sighing, being unable to relax, or feeling excessively tense? Severity: 1 2 3 Distress: 0 1 2 3 4 5
Elation or euphoria	Yes No	Does the patient appear to feel too good or act excessively happy? Severity: 1 2 3 Distress: 0 1 2 3 4 5
Apathy or indifference	Yes No	Does the patient seem less interested in his or her usual activities and in the activities and plans of others? Severity: 1 2 3 Distress: 0 1 2 3 4 5
Disinhibition	Yes No	Does the patient seem to act impulsively? For example, does the patient talk to strangers as if he or she knows them, or does the patient say things that may hurt people's feelings? Severity: 1 2 3 Distress: 0 1 2 3 4 5
Irritability or lability	Yes No	Is the patient impatient and cranky? Does he or she have difficulty coping with delays or waiting for planned activities? Severity: 1 2 3 Distress: 0 1 2 3 4 5
Motor disturbance	Yes No	Does the patient engage in repetitive activities, such as pacing around the house, handling buttons, wrapping string, or doing other things repeatedly? Severity: 1 2 3 Distress: 0 1 2 3 4 5
Nighttime behaviors	Yes No	Does the patient awaken you during the night, rise too early in the morning, or take excessive naps during the day? Severity: 1 2 3 Distress: 0 1 2 3 4 5
Appetite and eating	Yes No	Has the patient lost or gained weight, or had a change in the food he or she likes? Severity: 1 2 3 Distress: 0 1 2 3 4 5

Cummings J. *J Geriatr Psychiatry Neurol*. 2020;33(2):73–84.

Step 4 – Assess Body, Brain, and Mind

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 changes

Physical / Neurological Exam: Look for sources of pain and infection

Mental Status Exam: Look for changes from baseline such as increased confusion or disorganization, anxious or depressed affect, hyperactivity, disinhibition, paranoia, misidentifications, paranoia or other mental disturbances

Specific Causes and Exacerbating Factors

MEDICAL / PSYCHIATRIC	PSYCHOLOGICAL	ENVIRONMENTAL
Delirium	Fears	Temperature too hot or cold
Infection	Unmet needs (hunger, thirst)	Excessive noise or light
Metabolic disturbances	Boredom / needs attention	Unpleasant odors
Trauma	Grief	Inadequate caregiving
Pain / discomfort	Overstimulation	Lack of structure/ routine
Anxiety / phobias	Sleep disturbances	Lack of activities
Depression	Desire to escape / elope	Unfamiliar / confusing location
Mania	Feels lost or lonely	Disruptive staff or residents
Psychosis	Feels neglected or abused	
Medications (eg, steroids, narcotics,dopainergic)		
Substances (alcohol)		

Step 5 – Develop an Initial Formulation

- A formulation tells you what is happening and why it might be happening
- It identifies and describes the person (as a person, first and foremost) and their interests and habits
- It incorporates historical and baseline factors including relevant diagnoses and psychological factors
- It speaks to the underlying neurocognitive disorder, its course and associated neuropsychiatric symptoms
- It describes the care partner's role / other caregivers' roles and the overall care environment
- It details the agitated behaviors and offers hypotheses on the most salient aspects
- This formulation naturally leads to the best treatment plan

Key Questions

Is there a missing diagnosis?

- (eg, occult mania)

Is this the right environment

- (eg, a person in assisted living needs memory care)

Is this the right caregiver?

- (eg, the primary caregiver(s) is/are exhausted, neglectful, inadequate, unmotivated, etc.)

Key Learning Points

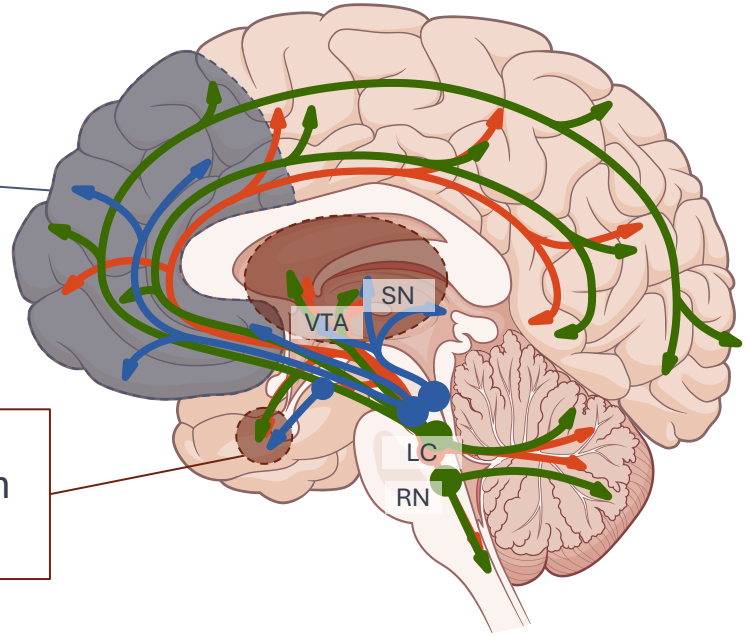
- Before making a diagnosis of Alzheimer's with agitation, make sure to rule out differential diagnoses
- Use the updated "buddy" coding per ICD-10 for Alzheimer's disease and the behavioral identifier
- There are many assessment tools and checklists available to evaluate agitation and behaviors in patients with dementia
  - Cohen-Mansfield Agitation Inventory (CMAI) – filled out by caregiver
  - Neuropsychiatric Inventory (NPI) – looks at different aspects of behaviors

Pathophysiology of AAD

The Pathophysiology of Agitation

AAD may reflect an imbalance between top-down **executive control** and bottom-up **emotional drive**

PFC function
(executive control)



Amygdala function
(emotional drive)

Dysfunction of NSD neurotransmitter system may contribute to imbalance between **executive control** and **emotional overdrive**

Norepinephrine system
Overactivity[4]

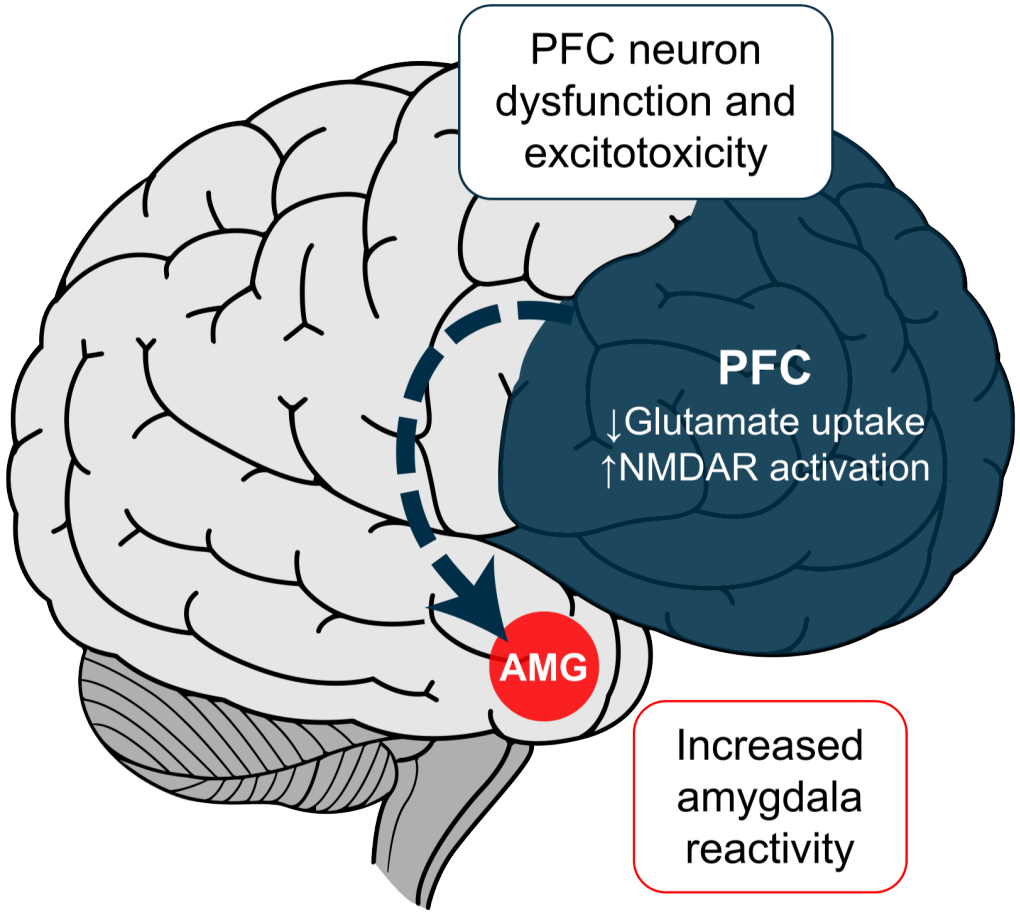
Serotonin system
Deficits[6]

Dopamine system
Dysregulation[9]

LC=locus coeruleus; NSD=norepinephrine, serotonin, dopamine; PFC=prefrontal cortex; RN=raphe nuclei; SN=substantia nigra; VTA=ventral tegmental area.

Rosenberg PB, et al. *Mol Aspects Med*. 2015;43-44:25-37. Banno K, et al. *Neuropsychiatr Dis Treat*. 2014;10:339-348. Wright CI, et al. *Biol Psychiatry*. 2007;62(12):1388-1395. Jacobs HI, et al. *Mol Psychiatry*. 2021;26(3):897-906. Arnsten AF, et al. *Neurobiol Stress*. 2015;1:89-99. Lanctôt KL, et al. *J Neuropsychiatry Clin Neurosci*. 2001;13(1):5-21. Evers EA, et al. *Curr Pharm Des*. 2010;16(18):1998-2011. Duke AA, et al. *Psychol Bull*. 2013;139(5):1148. Cox SM, et al. *Br J Psychiatry*. 2011;199(5):391-397. Lindenmayer JP. *J Clin Psychiatry*. 2000;61(14):5-10.

The Role of Glutamate in AAD



Aβ oligomers disrupt NMDA receptor signaling and impairs glutamate transporters on astrocytes, which results in increased synaptic glutamate

Extrasynaptic GluN2B-rich NMDARs are overactivated, which can lead to leading to both dendritic spine loss and potential neurotoxicity

Hypothesis: excess extrasynaptic glutamate impairs PFC function, leading to weaker control over the amygdala, which may manifest clinically as agitation.

Liu J, et al. *Front Neuroscience.* 2019;13:43. Cummings JL, et al. *CNS Spectrums.* 2024:1-10.

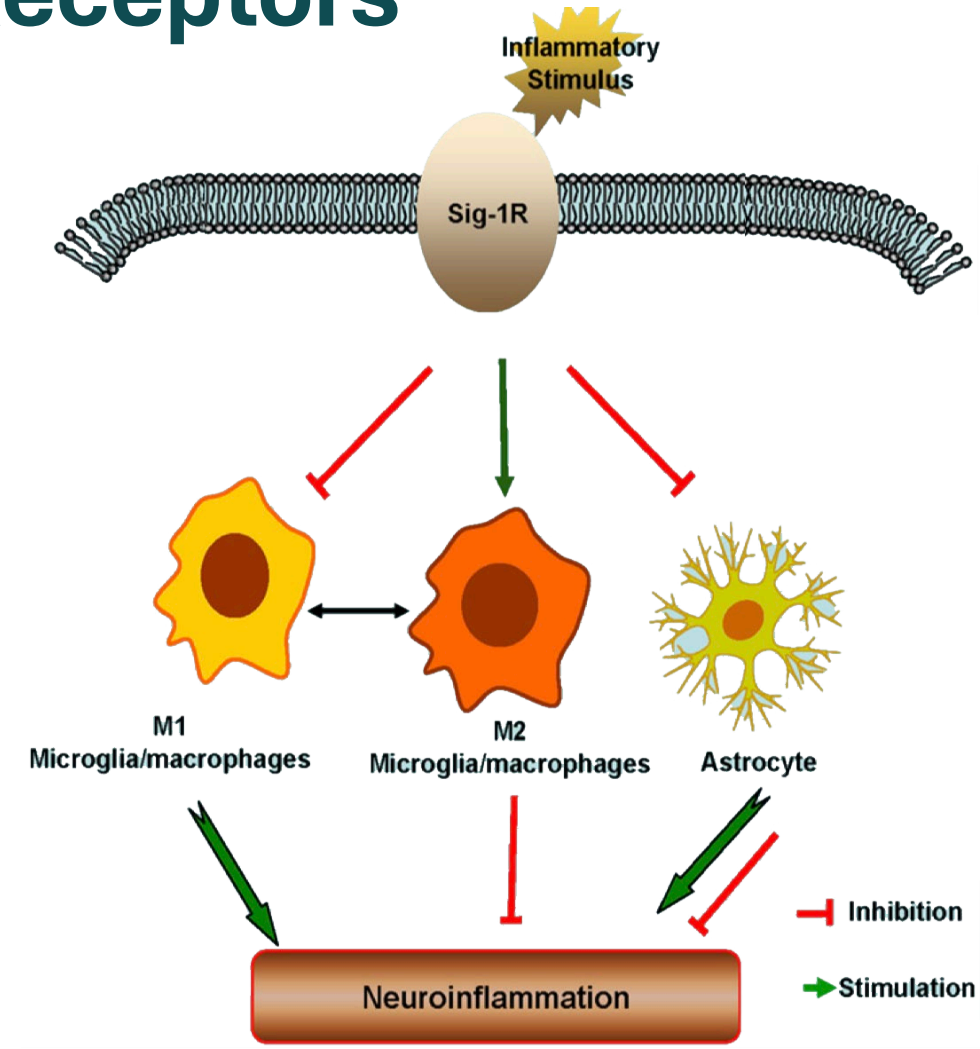
Role of Sigma-1 Receptors

Sigma-1 receptors are found on the endoplasmic reticulum and their activation reduces neuroinflammation and may improve circuit functions which influence behavioral outputs.

They also modulate NMDA receptor function in a way that limits excitotoxicity and may rebalance the ratio of excitation to inhibition of cortical circuits

Human PET scans in people with Alzheimer's show significantly reduced Sig-1R density across regions of the cortex in early AD

This relative Sig-1 receptor deficit state may increase vulnerability to excitotoxic and inflammatory injury



Ryskamp DA, et al. *Front Neurosci*. 2019;13 :474181. Jia J, et al. *Front Cellular Neurosci*. 2018;12:314. Mishina M, et al. *Ann Nuclear Med*. 2008;22(3):151-156.

How Do Neurocognitive Disorders Shape Agitation?

Dementia	Features
Alzheimer's Disease	Agitation is more common in middle and later stages of disease
Vascular Dementia	• Frontal and temporal lesions can cause disinhibition • Frontal and 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

Key Learning Points

- Glutamate dysfunction is a core feature of Alzheimer’s Disease
- Loss of glutamate synapses and hypofunction of NMDA receptors contributes to cognitive and behavioral symptoms, including agitation
- In Alzheimer’s Disease, sigma-1 receptor dysfunction causes neurodegeneration, showing evidence that sigma-1 receptor agonists can exert neuroprotective benefits

Pharmacologic Management of AAD

When are Medications Needed?

Dangerous or severe symptoms

Behavioral approaches are not working

Underlying psychiatric disorder (eg, bipolar disorder)

Psychotic symptoms

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.

Treatment Dilemmas

- Until recently, there was no universally recognized or FDA-designated indication for agitation or psychosis associated with dementia, or general BPSD
- Almost all psychotropic medication use is thus considered "off-label"
- Clinical trials have used variable methodologies and yielded high placebo responses
- It was not until 2023 that brexpiprazole became the first agent approved by the FDA for "agitation associated with dementia due to Alzheimer's disease"

BPSD = behavioral and psychological symptoms of dementia.

Kindermann SS, et al. *Drugs Aging*. 2002;19(4):257-276. Ballard C, et al. *Cochrane Database Syst Rev*. 2006;(1):CD003476; FDA press release 11 May 2023.

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 • 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 • Work over time and are generally safe and well tolerated	• 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	Poor to no efficacy, especially in acute situations

Common Side Effects

- Sedation
- Cognitive slowing / confusion
- Orthostasis
- Unsteady gait and falls
- Fractures
- Extrapyramidal symptoms
- Cardio- and cerebrovascular events
- Metabolic effects (increased glucose, lipids and prolactin levels)

Aigbogun MS, et al. *J Alzheimer's Dis*. 2020;77(3):1181-1194. Schneider LS, et al. *Am J Geriatr Psychiatry*. 2006;14(3):191-210. Rabins PV, et al. *Am J Psychiatry*. 2007;164(12):5-56. Porsteinsson AP, et al. *JAMA*. 2014;311(7):682-691. Caraci F, et al. *F1000Res*. 2020;9:F1000 Faculty Rev-686. Marcinkowska M, et al. *CNS Drugs*. 2020;34(3):243-268. Harding R, et al. *Med Law Rev*. 2012;21(2):243-277.

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	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)

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	-	-	-	-
Brexpiprazole	Grossberg et al.	433 / 270	73.7 -74.1	12	2 mg dose > placebo in both fixed and flexible dosed protocols

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.

Antipsychotics: A Review of Meta-Analyses

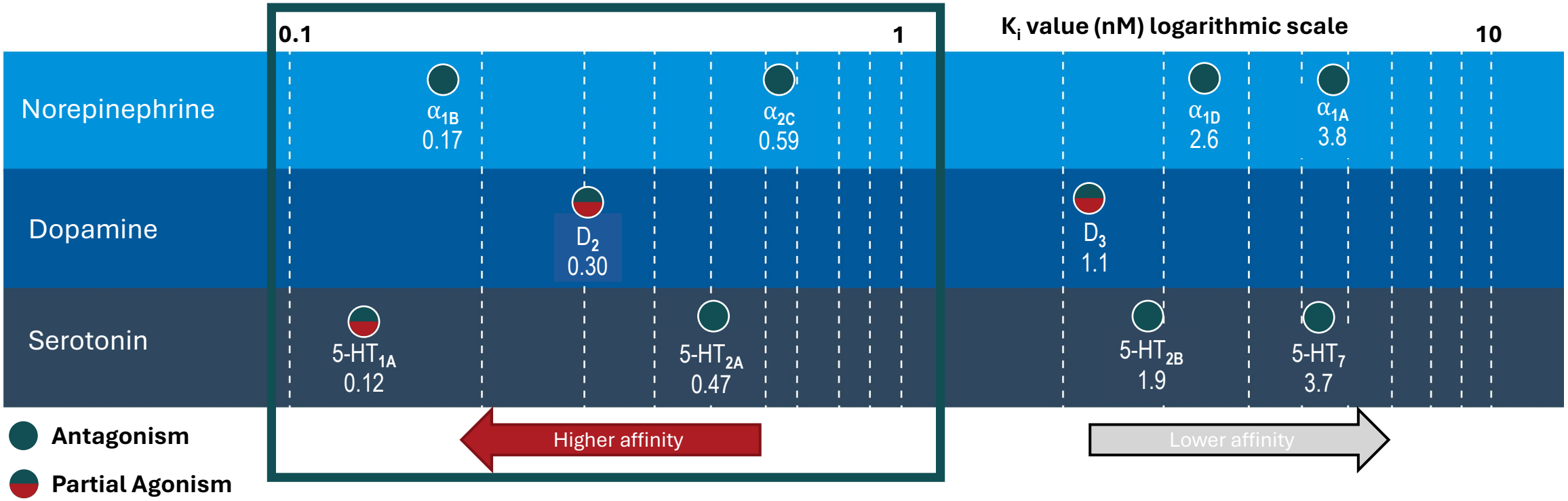
- Tampi et al. point out the basic challenges of antipsychotics: they are frequently used, especially in long-term care, but with limited monitoring, variable efficacy, and moderate to high risk of side effects
- Review of meta-analysis
  - Risperidone, olanzapine, and aripiprazole have modest benefits 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

EPS = extrapyramidal symptoms.

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

Pharmacologic Rationale for Brexpiprazole as a Potential Treatment for AAD

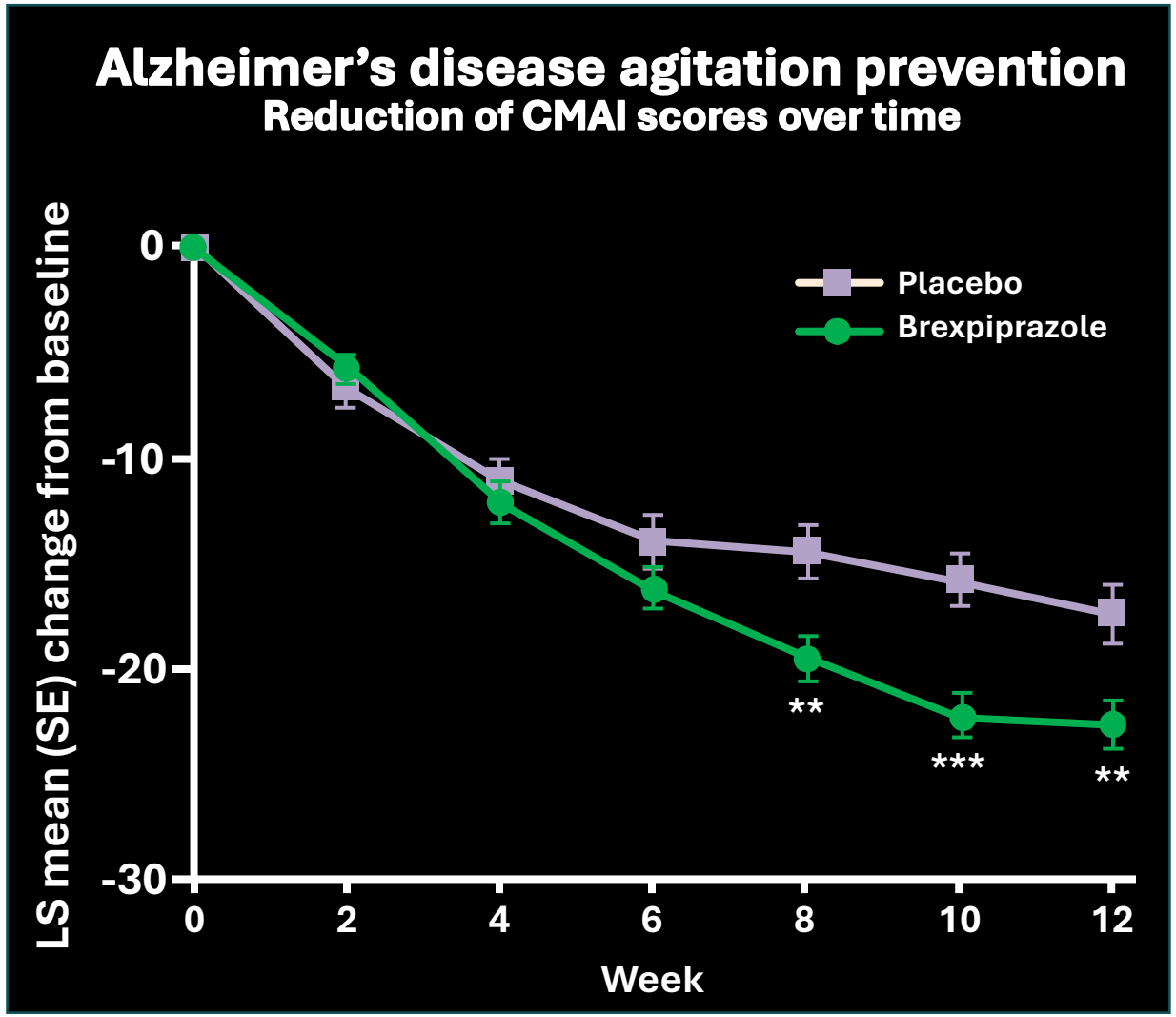
Has high binding affinity for norepinephrine, serotonin, and dopamine receptors



Binding affinity data shown are in-vitro.

Maeda K, et al. *J Pharmacol Exp Ther*. 2014;350(3):589-604.

Brexpiprazole



- In 2023 became the first FDA-approved drug to treat agitation associated with dementia due to Alzheimer's disease
- It is not FDA-indicated for patients with psychosis without agitation and carries the same Black box warning for mortality in elderly patients as other antipsychotics
- In clinical trials it demonstrated statistically significant improvement in total CMAI at Week 12
  - Brexpiprazole 2 mg dose: Placebo-adjusted improvement −3.77 from baseline (*P* = .04)

LS = least squares; SE = standard error.
Grossberg G, et al. *Am J Geriatr Psychiatry*. 2020;28(4):383-400.

Atypical Antipsychotics: *Mortality Warning*

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

- Listed for elderly patients with dementia-related psychosis
- Analyses of 17 placebo-controlled trials revealed risk of death in drug-treated patients between 1.6 and 1.7x that seen in placebo-treated patients (4.5% vs 2.6%)
- Most deaths were 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 the trend of increased mortality appeared in 15 out of 17 studies

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

Risk Management with Antipsychotics

- Off-label usage is permitted but should be based on scientific support and professional standards of care
- Documentation must provide the clinical rationale for use and recognition that risks outweigh benefits
- Documentation should include discussion with patient and/or legally authorized representatives; consent forms have been proposed
- Follow appropriate dosing and management, including frequent re-assessment and attempts at discontinuation
- Avoid inappropriate uses such as for insomnia or anxiety, or on a PRN basis in nursing homes
- Always have a well-documented, recently-completed comprehensive psychiatric assessment that details the diagnostic assessment with reference to DSM-5 criteria

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

Antidepressants

Drug	N	Weeks	Outcome
Citalopram vs placebo	186	9	CitAD: 10 -30 mg dosing range showed significant improvement over placebo; some QT prolongation and cognitive slowing seen which may limit dosing
Escitalopram vs placebo	588 proj	24	S-CitAD trial : results pending
Mirtazapine vs placebo	204	12	No improvement over placebo
Sertraline vs placebo	22	4	Significant improvement on agitation, aggression, irritability
Sertraline vs placebo augmentation of donepezil	144	12	No significant difference overall ; Moderate–severe group showed 60% vs 40% improvement
Trazodone vs haloperidol	149	16	No difference between agents and behavioral management; 34% improvement rate overall

CitAD = Citalopram for Agitation in Alzheimer Disease; S-CitAD = Escitalopram for Agitation in Alzheimer's Disease.

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. Banerjee et al. *Lancet*. 2021;398(10310):1487-1497. Porsteinsson AP, et al. JAMA. 2014;311(7):682-91. Ehrhardt S, et al. *Alzheimers Dement*. 2019;15(11):1427-1436.

AXS-05

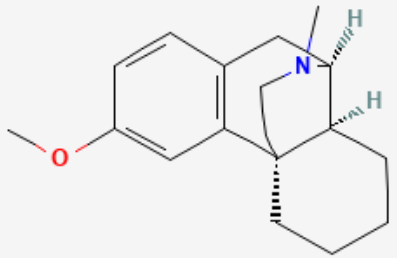
- AXS-05 is a novel antidepressant composed of a combination of dextromethorphan and bupropion (DXM/BUP 45mg/105mg) approved by the FDA in 2022 for Major Depressive Disorder. It has been studied for agitation associated with Alzheimer's disease (AAD) in four pivotal studies.
- The submission to the FDA is supported by data from 4 completed Phase 3 studies (ACCORD-1, ACCORD-2, ADVANCE-1, and ADVANCE-2)
- The FDA granted breakthrough status in June 2020 to AXS-05 for AAD
- The plan for NDA submission to the FDA is the third quarter 2025

Ward K, Citrome L. *Expert Opin Investig Drugs*. 2022 Aug;31(8):773-780.

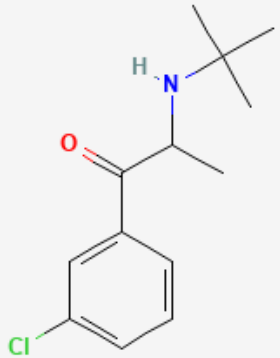
DXM-BUP:

Exploring the Key Components

Dextromethorphan



Bupropion



NMDA receptor antagonist

1. Increases glutamate release by decreasing presynaptic inhibition
2. Redirecting synaptic glutamate to AMPA
3. Removing inhibitory signal of extrasynaptic NMDA receptors

Sigma-1 receptor agonist

1. Fine-tunes monoamine and glutamatergic signaling
2. Reduces neuroinflammation and promotes neuronal repair and regeneration
3. Helps degrade misfolded proteins and dampen glutamate excitotoxicity

(Relatively) weak inhibitor of NE and DA reuptake

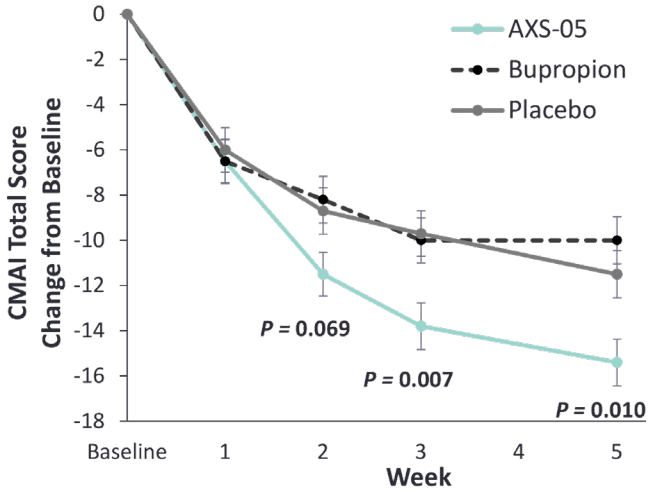
Increases and prolongs the plasma concentration of DXM

DXM-BUP = dextromethorphan/bupropion; NMDA = N-methyl-D-aspartate; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NE = norepinephrine; DA = dopamine.

Stahl SM. *CNS Spectr*. 2019;24(5):461-466.

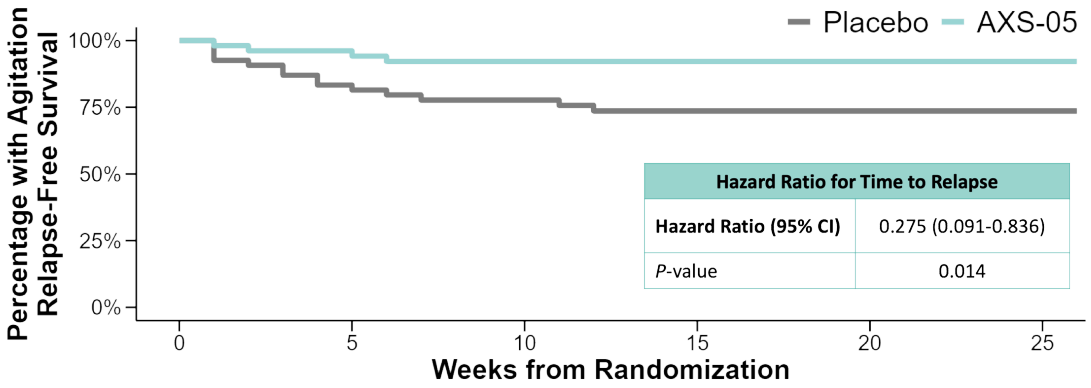
AXS-05 Phase 3 Clinical Data in AAD

ADVANCE-1: Reduction in CMAI

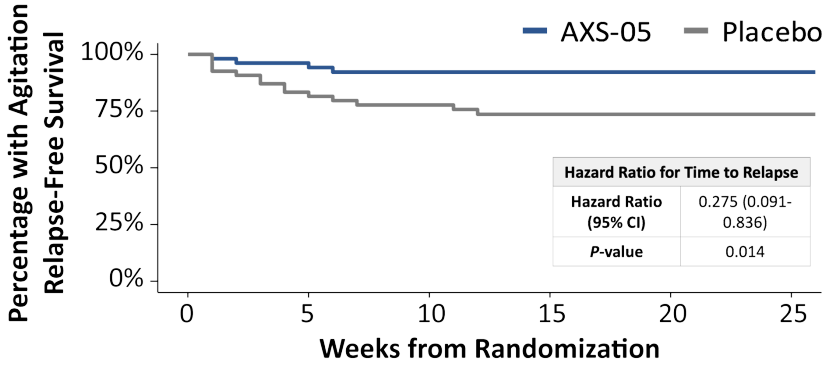


ADVANCE-1	ADVANCE-2	ACCORD-1	ACCORD-2
Acute Efficacy Study 5 weeks, N=366	Acute Efficacy Study 5 weeks, N=408	Randomized Withdrawal Study Up to 26 wks, N=108	Randomized Withdrawal Study Up to 24 wks, N=167
Primary Endpoint: Mean reduction from baseline in CMAI total score at Week 5 AXS-05: **15.4 points** placebo: **11.5 points** **p = 0.010**	**Primary Endpoint:** Mean reduction from baseline in CMAI total score at Week 5 AXS-05: **13.8 points** Placebo:**12.6 points** **p = 0.380**	**Primary Endpoint:** Time to relapse **hazard ratio of 0.275**; **p = 0.014**	**Primary Endpoint:** Time to relapse **hazard ratio of 0.276**; **p = 0.001**

ACCORD-1: Time to Relapse



ACCORD-2: Time to Relapse



Clinical Profile of AXS-05 (Dextromethorphan-Bupropion) in Treating Alzheimer's Disease Agitation: Results From the Phase 2/3 Development Program. Poster Presented at Psych Congress, October 29 – November 2, 2024. Boston, MA. Cummings J, et al. Efficacy and Safety of AXS-05 in Alzheimer's Disease Agitation: Results From ACCORD-2, a Phase 3 Randomized Withdrawal Double-Blind Placebo-Controlled Study. Poster Presented at American Academy of Neurology Annual Meeting April 5–9, 2025 San Diego, CA.

AXS-05: Common Adverse Events

- Most commonly reported adverse events include **dizziness, diarrhea, falls, dry mouth, and somnolence**
- Overall tolerability was favorable with low incidence of serious adverse events
- Most adverse events did not require discontinuation of therapy compared with placebo

Ward K, Citrome L. *Expert Opin Investig Drugs*. 2022 Aug;31(8):773-780.

Mood Stabilizers (anticonvulsants)

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 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
Prazosin (α-blocker)	Prazosin has been found useful in reducing agitation in several studies
Trazodone	May be safer alternative to benzodiazepines for short-term reduction in agitation
Dextromethorphan-Quinidine	Indicated for pseudobulbar palsy. Modest evidence showing behavioral improvement in agitation in one study; clinical trial of deuterated form AVP-786 did not meet endpoints
Dexmedetomidine	a2-adrenergic agonist is a quick-acting sublingual tablet in ~2 hours, with FDA-indication for agitation in schizophrenia and bipolar disorder
Dronabinol	Early data showing positive results

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. Smith, et al. *Clin Psychopharmacol Neurosci*. 2023;21(2):215-221. Cummings JL, et al. Study presented at: 16th Clinical Trials on Alzheimer Disease. October 24-27, 2023. Press Release, Otsuka, February 12, 2024, https://www.otsuka-us.com/news/otsuka-announces-phase-3-topline-results-avp-786-treatment-agitation-associated-dementia-due. Accessed September 15, 2025.

THC (delta-9-tetrahydrocannabinol) for AAD (Off-Label)

Nabilone is a synthetic oral analogue of THC used to treat nausea and vomiting associated with chemotherapy. It is FDA approved in the US; it showed significant improvement vs placebo on CMAI in a small 14-week randomized, double-blind crossover trial

Treatment-Emergent Adverse Events ≥5%

(N=38)	Nabilone Phase	Placebo Phase
Sedation/lethargy	45%	16%
Treatment-limiting sedation	13%	3%
Falls	21%	18%
Discontinuation due to SAE	13%	11%

Dronabinol is a synthetic oral analogue of THC that is also FDA-approved for nausea and vomiting associated with chemotherapy and for anorexia / wt loss in AIDS patients. A recent study compared it to placebo in a three-week treatment study for agitation associated with AD and found an average 30% reduction on the Neuropsychiatric Inventory.

THC = tetrahydrocannabinol; SAE = serious adverse event.

Herrmann N, et al. *Am J Geriatr Psychiatry*. 2019;27(11):1161-1173. Wang LY, et al. *Am J Geriatr Psychiatry*. 2009;17(9):744-751. Rosenberg RB et al. *Alzheimer's & Dementia*. 2023; 19(S4).

Prazosin-Mechanism of Action

- What causes Alzheimer's dementia agitation is due to increased norepinephrine in the central nervous system
- Prazosin does not have an FDA indication, but studies show that it works by blocking norepinephrine effects in the central nervous system at the postsynaptic alpha-1 adrenoreceptors
- Prazosin is the only available alpha-1 adrenoreceptor blocker that crosses from the blood into the brain

Wang LY, et al. *Am J Geriatr Psychiatry*. 2009;17(9):744-51.

Clinical Data Supporting Prazosin in Alzheimer's Disease Agitation

- Double-blind, placebo-controlled, parallel-group study
- 11 participants in the prazosin group and 11 participants in the placebo group
- Participants were from a nursing home and community-dwelling
- Doses of prazosin were started at 1 mg at bedtime and titrated up to a maximum dose of 2 mg every morning and 4 mg at bedtime
- Primary endpoints: change in the BPRS and NPI
- Secondary endpoint: change in the Clinical Global Impression of Change Scale (CGIC)
- Results: Participants in the prazosin arm had a decrease in Alzheimer's Agitation compared to placebo, without worsening hypotensive effects compared to placebo

Wang LY, et al. *Am J Geriatr Psychiatry*. 2009;17(9):744-51.

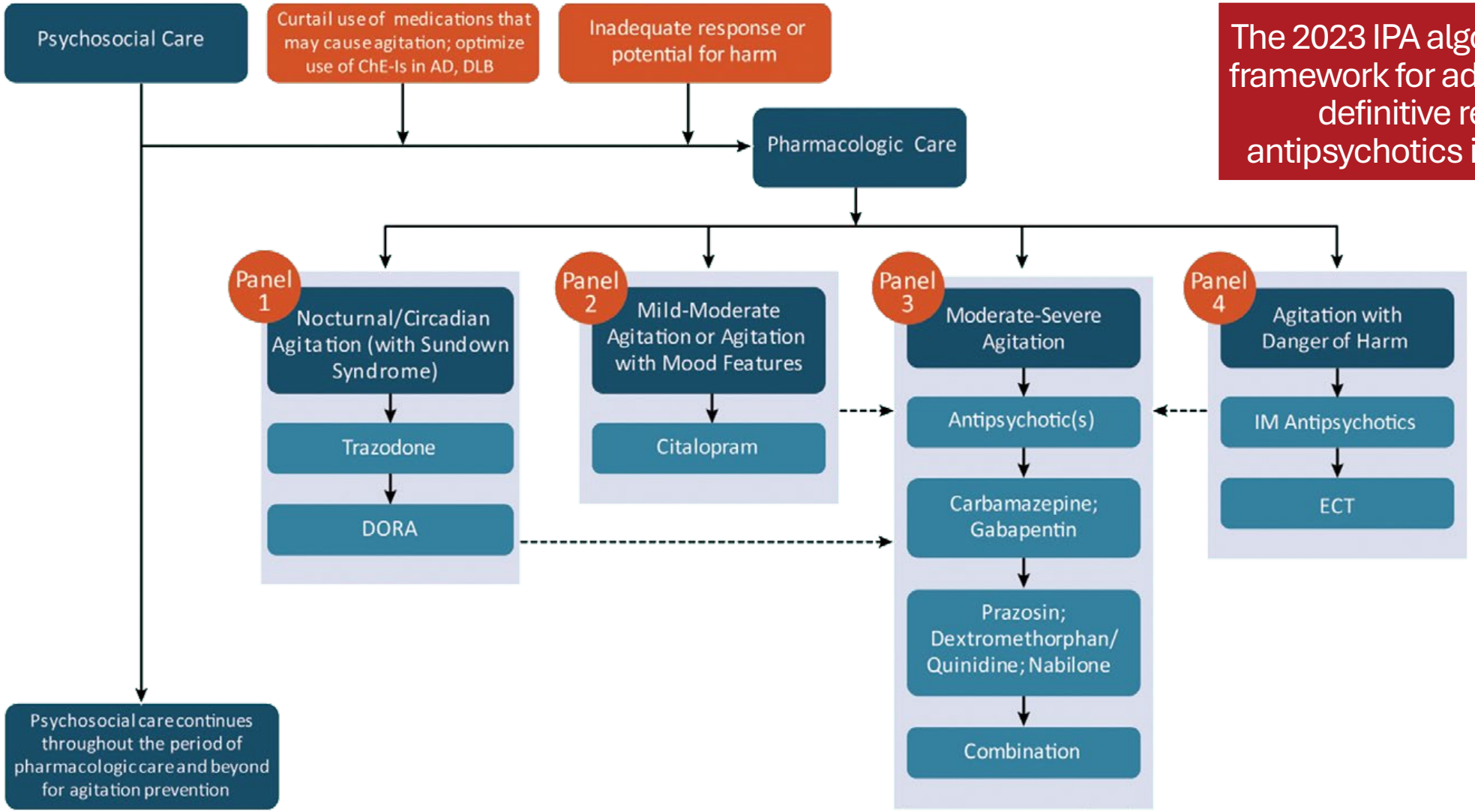
Electroconvulsive Therapy (ECT)

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

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

IPA 2023 Algorithm for Agitation in Alzheimer's



The 2023 IPA algorithm provides a modern framework for addressing AAD, including a definitive recommendation for antipsychotics in certain circumstances

DLB = dementia with Lewy bodies; DORA = dual orexin receptor antagonist; ECT = electroconvulsive therapy.

Cummings, J, et al. *Int Psychogeriatr.* 2024 Apr;36(4):251-262.

Key Learning Points

- Brexpiprazole was the first agent FDA approved for the treatment of AAD and is generally well-tolerated
- AXS-05 is a promising investigational therapy for AAD, showing delay in time to relapse in clinical trials, and was generally well-tolerated with a safety profile that is favorable to antipsychotics
- Off-label treatments offer modest efficacy, but can pose significant risks in this population

Faculty and Patient Caregiver Advocate Panel Discussion

- Monitoring and Documentation of Patient Response to Treatment
- Considerations for Optimal Management of AAD in LTC
- Nonpharmacological Approaches
- Caregiver Action Network Resources

References

Faculty and Patient Caregiver Advocate Panel Discussion

CAREGIVER ACTION NETWORK CAN

Caregiver Action Network
Resources for Agitation in Alzheimer’s

Navigating Alzheimer’s: Effective Caregiving Approaches for Neuropsychiatric Symptoms

Alzheimer’s Caregiver Summit: A Peer-Led Dive into Mood, Memory & More

Mastering Communication: Proven Strategies for Supporting Loved Ones with Cognitive Challenges

Alzheimer’s Disease Educational Video Series

Understanding Alzheimer's: Insight from a Caregiver's Heart

Caregiver Help Desk

Q&A