



**Alzheimer's Disease
& Cognitive Disorders**
VIRTUAL SYMPOSIUM

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Neuropsychiatric Symptoms in Alzheimer's Disease: Identification And Intervention across Disciplines

Marc Agronin, MD

*Chief Medical Officer Frank C. and Lynn Scaduto
MIND Institute at Miami Jewish Health*

Carolyn K. Clevenger, DNP, GNP-BC

*Professor, Nell Hodgson Woodruff School of Nursing
Director, Integrated Memory Care*

- **Marc Agronin, MD:** Grant/Research Support—Alzheon, Bristol Myers Squibb, Eli Lilly, IGC Pharma, Noah Pharmaceuticals, Suven; Speakers Bureau—Otsuka
- **Carolyn Clevenger:** Advisory Board—Axome, BrainCheck, Eli Lilly, Otsuka; Consultant—BrainCheck, Eli Lilly, Otsuka; Speakers Bureau—BrainCheck, Eli Lilly, Otsuka

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- Define AD agitation and psychosis, and describe their prevalence and clinical significance
- Implement strategies for timely, accurate recognition and assessment of AD agitation and psychosis
- Evaluate the MOAs, recent clinical evidence, and potential therapeutic implications associated with novel and emerging agents for AD agitation and psychosis

Introduction to Neuropsychiatric Symptoms

Neuropsychiatric Symptoms (NPS) Associated with Alzheimer's Disease

It is estimated that 80% to 90% of patients with neurocognitive disorders demonstrate various forms of NPS, with higher rates seen in more severe dementia and in nursing home populations.

DEPRESSION

MANIA

ANXIETY

AGITATION

APATHY

[Physical or Verbal]

PSYCHOSIS

Wandering – Excessive motor activity – Intrusiveness

Resistance – Disinhibition – Sleep Disturbances

The Burden of Neuropsychiatric Symptoms

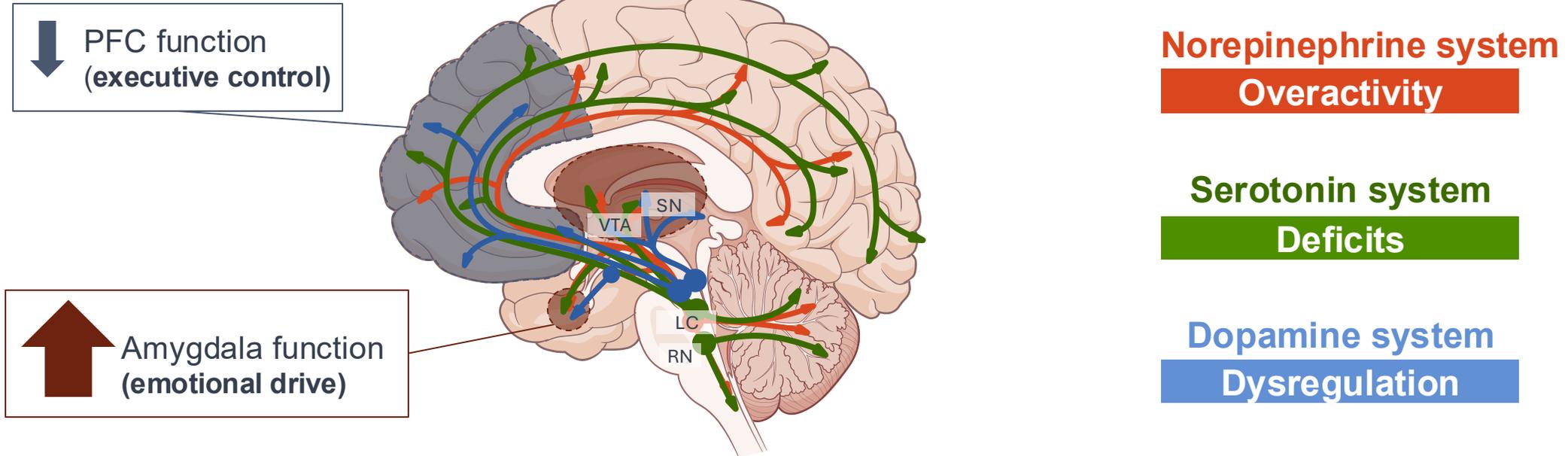
A tremendously negative impact on daily life and disease course

- 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)

The Pathophysiology of Neuropsychiatric Symptoms

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

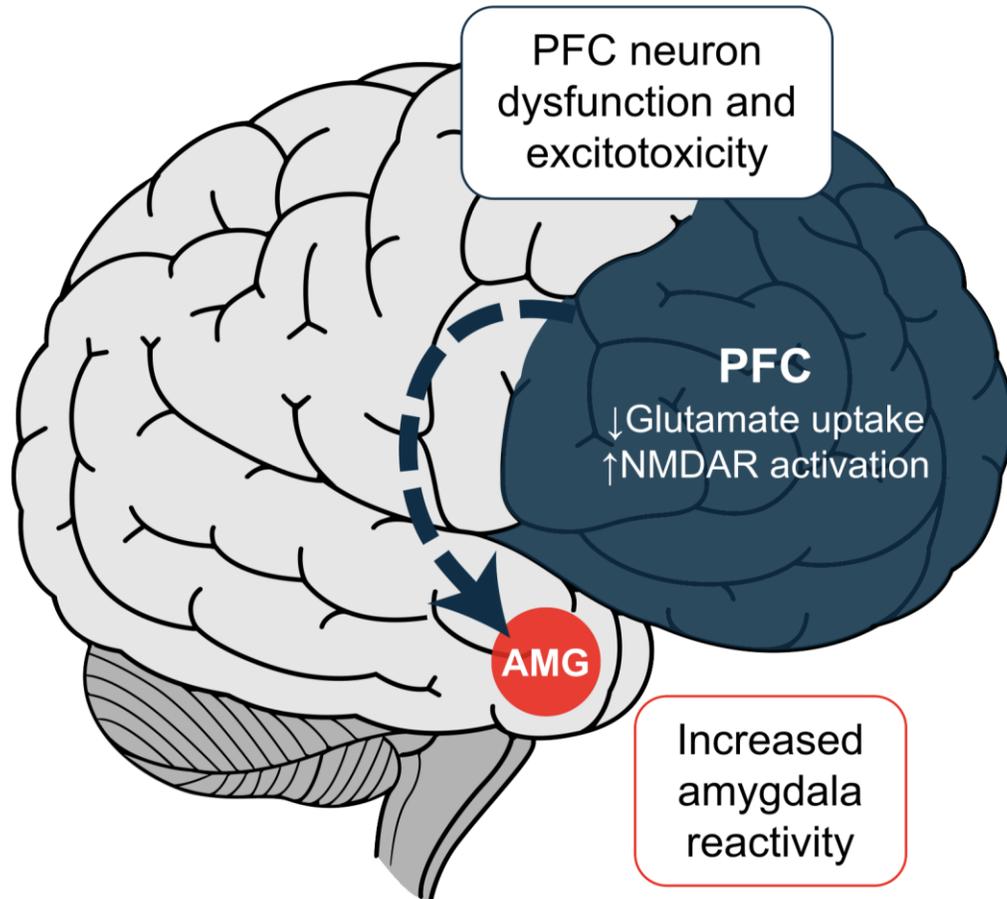
Dysfunction of NSD neurotransmitter system may contribute to imbalance between **executive control** and **emotional overdrive**



AAD = affective attention dysregulation; 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



$A\beta$ oligomers disrupt NMDA receptor signaling and impair 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.

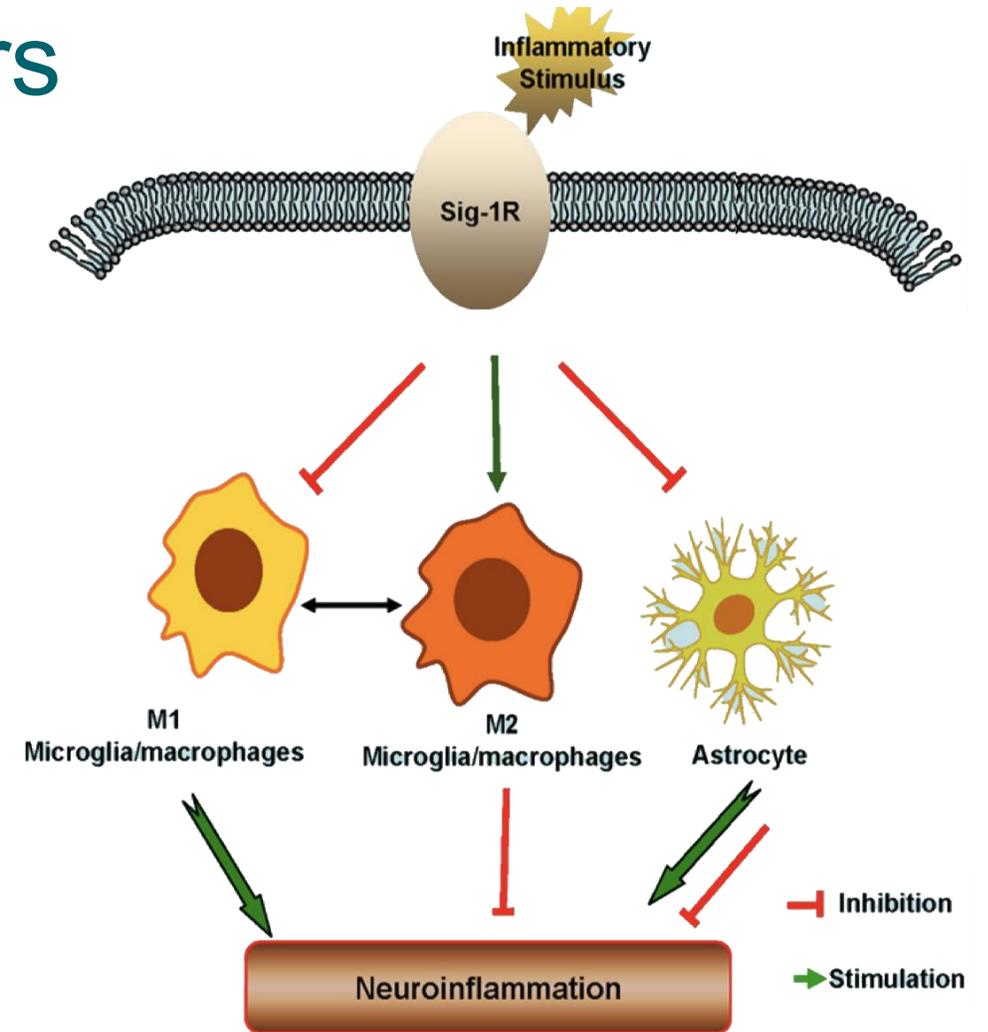
The Role of Sigma-1 Receptors

Sigma-1 receptors are found on the endoplasmic reticulum and their activation reduces neuroinflammation and may improve circuit functions that 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



How Do Different Neurocognitive Disorders Shape Neuropsychiatric Symptoms?

Dementia	Features
Alzheimer's Disease	Agitation is more common in middle and later stages of disease
Vascular Dementia	<ul style="list-style-type: none"> • 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

Care Partners Are Key

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



Key Learning Points

- NPS has key roots in brain circuitry and physiology related to an imbalance between emotional drive and executive function
- Disruptions to key pathways mediated by serotonin, norepinephrine, dopamine, and glutamate underlie many NPS
- Sigma-1 receptors are involved in neuronal inflammation and glutamate activity
- The form of damage to the brain varies by dementia type and influences the presentation of agitation

Detection and Diagnosis

DICE: A Diagnostic and Treatment Algorithm

Developed for agitation, but can apply to all NPS

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

Step 1 – Assess for Safety First

Don't ignore acute symptoms. The following symptoms warrant immediate identification and intervention, sometimes with ER assessment and hospitalization

- Delirium
- Assaultiveness
- Threatening or homicidal threats
- Suicidal threats, gestures, plans, attempts
- Self-neglect

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, and 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?

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, 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, dopaminergic)		
Substances (alcohol)		

Challenges to Assessment

- NPS are sometimes intermittent and unpredictable
- Patients often cannot provide accurate history
- Care partner, staff, and documented reports may be variable, inaccurate, and subject to interpretation
- Without direct observation, relevant factors can be missed
- Scales can be useful, but require time and training

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

- A systematic approach is essential to identifying NPS
- Take a holistic perspective on the patient, learning about them as a person, including their medical history and social history
- Detailed assessment might reveal relevant causes, triggers, or influential factors

Agitation & Psychosis: Identification and Assessment

What Is Alzheimer's Disease Agitation?

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

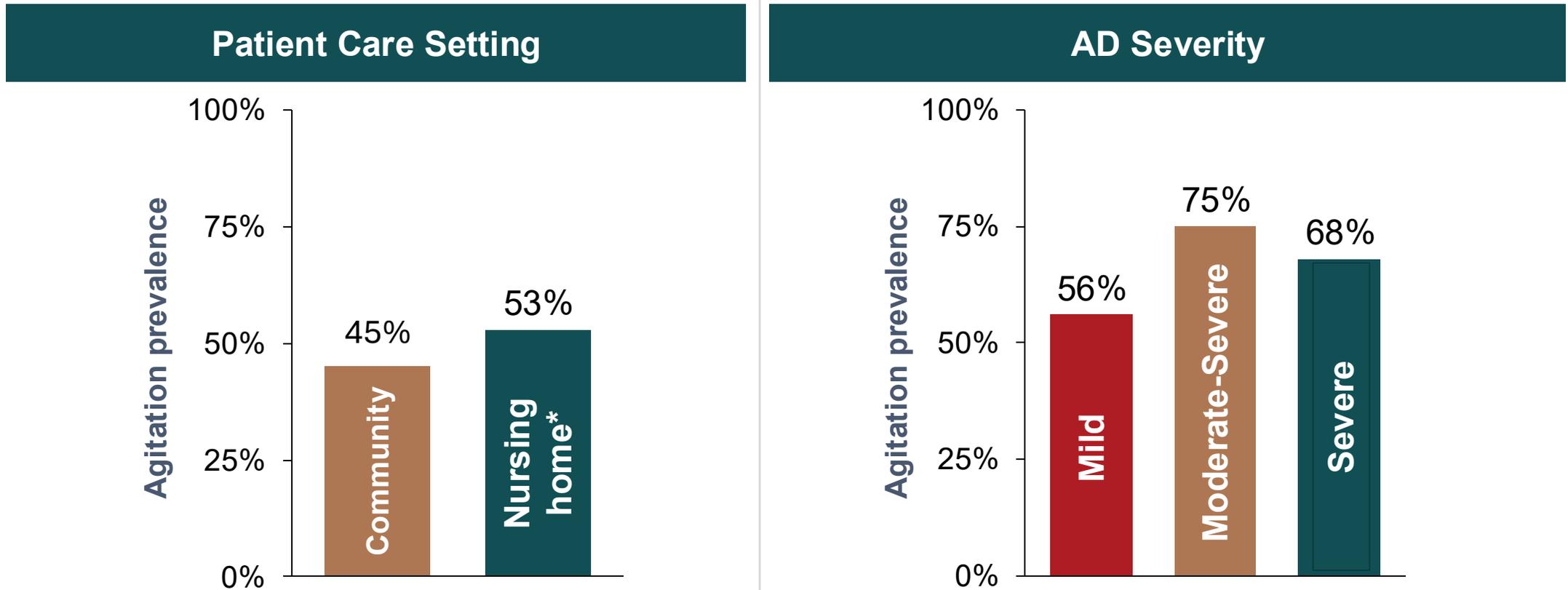
1. The patient meets the criteria for cognitive impairment or a dementia syndrome
2. The patient exhibits **≥ 1 agitation behavior(s)** with emotional distress that is persistent or frequently recurrent for **≥ 2 weeks**, or the behavior represents a dramatic change from the patient's usual behavior
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

The Spectrum of Agitated Behaviors

PHYSICAL AGGRESSION	VERBAL AGGRESSION	EXCESSIVE MOTOR ACTIVITY
Grabbing	Yelling	Pacing
Shoving / Pushing	Speaking excessively loudly	Rocking
Resisting	Using profanity	Gesturing
Hitting or kicking others	Screaming	Pointing fingers
Scratching / Biting	Shouting	Restlessness
Throwing objects	Threatening	Repetitive mannerisms
Hitting self		Intrusive wandering
Slamming doors		
Tearing things		
Destroying property		



Agitation Associated with AD Is Highly Prevalent Across Patient Settings and Disease Severity



*Nursing home percentage reported includes patients with AD and other dementias.

What is Alzheimer's Disease Psychosis?

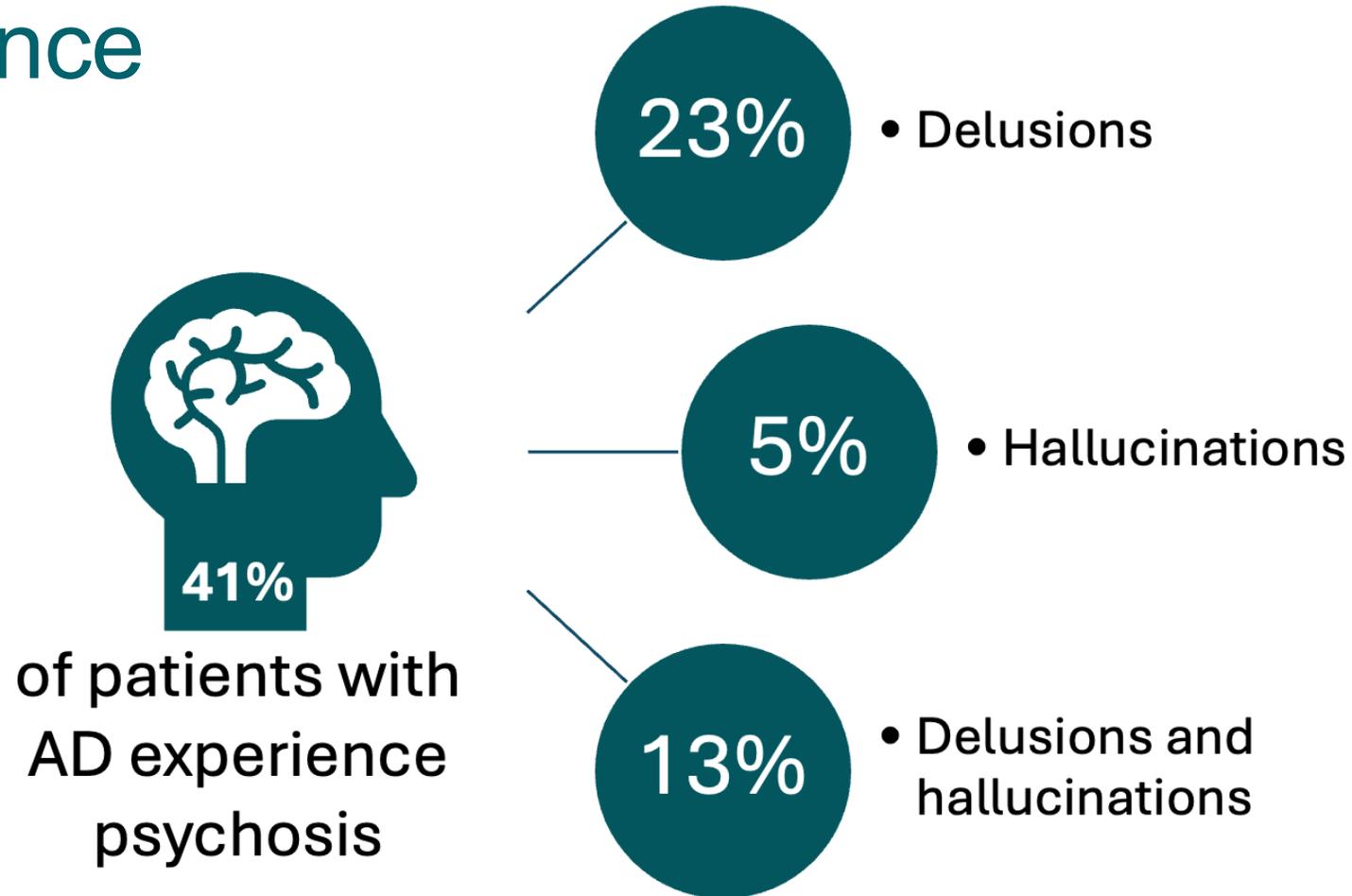
- Psychosis can include delusions, hallucinations, or both
- Patients of older age, with comorbid depression and aggression, are more likely to experience delusions
- Patients with more severe dementia and longer duration of AD are more likely to experience hallucinations

The Spectrum of Psychotic Symptoms

Delusions	Hallucinations
<ul style="list-style-type: none"> • Paranoid <ul style="list-style-type: none"> – Items are being stolen – Caregiver wants to harm person – Spouse is having an affair • Misidentification <ul style="list-style-type: none"> – House is not one's own – Spouse is someone strange – Someone strange in the mirror • Somatic <ul style="list-style-type: none"> – Persistent, unusual symptom – Parasitic infestation 	<ul style="list-style-type: none"> • Visual <ul style="list-style-type: none"> – Seeing people (large or small) – Seeing insects or animals • Auditory <ul style="list-style-type: none"> – Voices – Noises – Music • Olfactory and tactile are less common and typically have specific medical causes, eg, <ul style="list-style-type: none"> – Seizures – Substance withdrawal



Prevalence



Screening & Assessment Tools

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)

Assessment instruments focused on PSYCHOSIS

- Scale for The Assessment Of Positive Symptoms (SAPS - H+D)

NPI = Neuropsychiatric Inventory; BEHAVE-AD = Behavioral Pathology in AD Rating Scale; ABID = Agitated Behavior in Dementia; BARS = Brief Agitation Rating Scale; CMAI = Cohen-Mansfield Agitation Inventory; DBRS = Disruptive Behavior Rating Scales; PAS = Pittsburgh Agitation Scale; SOAPD = Scale for Observation of Agitation in Persons With Dementia.

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



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



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)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Kicking	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Grabbing onto people	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Pushing	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Throwing things	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Biting	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Scratching	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Spitting	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Hurt self or others	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. Tearing things or destroying property	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. Making physical sexual advances	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12. Paces, aimless wandering	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13. Inappropriate dress or disrobing	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14. Trying to get to a different place. .	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15. Intentional falling	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16. Eating/drinking inappropriate substances	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
17. Handling things inappropriately	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
18. Hiding things	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
19. Hoarding things	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
20. Performing repetitious mannerisms	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
21. General restlessness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
22. Screaming	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
23. Making verbal sexual advances ...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
24. Cursing or verbal aggression	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
25. Repetitive sentences or questions	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
26. Strange noises (weird laughter or crying)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
27. Complaining	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
28. Negativism	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
29. Constant unwarranted request for attention or help	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

SAPS CODES		
0 = None/Not at All	3 = Moderate	U = Unknown/ Cannot Be Assessed/
1 = Questionable	4 = Marked	Not Assessed
2 = Mild	5 = Severe	

Scale for The Assessment Of Positive Symptoms SAPS- H+D

See SAPS Manual for detailed coding definitions (N. Andreason, 1984)



	NONE	1	2	3	4	5	SEVERE
HALLUCINATIONS							
1. Auditory Hallucinations The patient reports voices, noises, or other sounds that no one else hears.	0	1	2	3	4	5	[17060]
2. Voices Commenting The patient reports a voice which makes a running commentary on his behavior or thoughts.	0	1	2	3	4	5	[17070]
3. Voices Conversing The patient reports hearing two or more voices conversing.	0	1	2	3	4	5	[17080]
4. Somatic or Tactile Hallucinations The patient reports experiencing peculiar physical sensations in the body.	0	1	2	3	4	5	[17090]
5. Olfactory Hallucinations The patient reports experiencing unusual smells which no one else notices.	0	1	2	3	4	5	[17100]
6. Visual Hallucinations The patient sees shapes or people that are not actually present.	0	1	2	3	4	5	[17110]
7. Global Rating of Hallucinations This rating should be based on the duration and severity of the hallucinations and their effects on the patient's life.	0	1	2	3	4	5	[17120]



	NONE	1	2	3	4	5	SEVERE
DELUSIONS							
8. Persecutory Delusions The patient believes he is being conspired against or persecuted in some way.	0	1	2	3	4	5	[17130]
9. Delusions of Jealousy The patient believes his spouse is having an affair with someone.	0	1	2	3	4	5	[17140]
10. Delusions of Guilt or Sin The patient believes that he has committed some terrible sin or done something unforgivable.	0	1	2	3	4	5	[17150]
11. Grandiose Delusions The patient believes he has special powers or abilities.	0	1	2	3	4	5	[17160]

	NONE	1	2	3	4	5	SEVERE	UNK
RELIGIOUS DELUSIONS								
12. Religious Delusions The patient is preoccupied with false beliefs of a religious nature.	0	1	2	3	4	5	[17170]	
SOMATIC DELUSIONS								
13. Somatic Delusions The patient believes that somehow his body is diseased, abnormal, or changed.	0	1	2	3	4	5	[17180]	
DELUSIONS OF REFERENCE								
14. Delusions of Reference The patient believes that insignificant remarks or events refer to him or have special meaning.	0	1	2	3	4	5	[17190]	
DELUSIONS OF BEING CONTROLLED								
15. Delusions of Being Controlled The patient feels that his feelings or actions are controlled by some outside force.	0	1	2	3	4	5	[17200]	
DELUSIONS OF MIND READING								
16. Delusions of Mind Reading The patient feels that people can read his mind or know his thoughts.	0	1	2	3	4	5	[17210]	
THOUGHT BROADCASTING								
17. Thought Broadcasting The patient believes that his thoughts are broadcast so that he himself or others can hear them.	0	1	2	3	4	5	[17220]	
THOUGHT INSERTION								
18. Thought Insertion The patient believes that thoughts that are not his own have been inserted into his mind.	0	1	2	3	4	5	[17230]	
THOUGHT WITHDRAWAL								
19. Thought Withdrawal The patient believes that thoughts have been taken away from his mind.	0	1	2	3	4	5	[17240]	
GLOBAL RATING OF DELUSIONS								
20. Global Rating of Delusions This rating should be based on the duration and persistence of the delusions and their effect on the patient's life.	0	1	2	3	4	5	[17250]	
BIZARRE BEHAVIOR								
CLOTHING AND APPEARANCE								
21. Clothing and Appearance The patient dresses in an unusual manner or does other strange things to alter his appearance.	0	1	2	3	4	5	[17260]	U
SOCIAL AND SEXUAL BEHAVIOR								
22. Social and Sexual Behavior The patient may do things considered inappropriate according to usual social norms (e.g., masturbating in public).	0	1	2	3	4	5	[17270]	U

	NONE	1	2	3	4	5	SEVERE	UNK
AGGRESSIVE AND AGITATED BEHAVIOR								
23. Aggressive and Agitated Behavior The patient may behave in an aggressive, agitated manner, often unpredictably.	0	1	2	3	4	5	[17280]	U
REPETITIVE OR STEREOTYPED BEHAVIOR								
24. Repetitive or Stereotyped Behavior The patient develops a set of repetitive actions or rituals that he must perform over and over.	0	1	2	3	4	5	[17290]	U
GLOBAL RATING OF BIZARRE BEHAVIOR								
25. Global Rating of Bizarre Behavior This rating should reflect the type of behavior and the extent to which it deviates from social norms.	0	1	2	3	4	5	[17300]	U
POSITIVE FORMAL THOUGHT DISORDER								
DERAILMENT								
26. Derailment A pattern of speech in which ideas slip off track onto ideas obliquely related or unrelated.	0	1	2	3	4	5	[17310]	
TANGENTIALITY								
27. Tangentiality The patient replies to a question in an oblique or irrelevant manner.	0	1	2	3	4	5	[17320]	
INCOHERENCE								
28. Incoherence A pattern of speech that is essentially incomprehensible at times.	0	1	2	3	4	5	[17330]	
ILLOGICALITY								
29. Illogicality A pattern of speech in which conclusions are reached that do not follow logically.	0	1	2	3	4	5	[17340]	
CIRCUMSTANTIALITY								
30. Circumstantiality A pattern of speech that is very indirect and delayed in reaching its goal idea.	0	1	2	3	4	5	[17350]	
PRESSURE OF SPEECH								
31. Pressure of Speech The patient's speech is rapid and difficult to interrupt; the amount of speech produced is greater than that considered normal.	0	1	2	3	4	5	[17360]	
DISTRACTIBLE SPEECH								
32. Distractible Speech The patient is distracted by nearby stimuli which interrupt his flow of speech.	0	1	2	3	4	5	[17370]	
CLANGING								
33. Clanging A pattern of speech in which sounds rather than meaningful relationships govern word choice.	0	1	2	3	4	5	[17380]	
GLOBAL RATING OF POSITIVE FORMAL THOUGHT DISORDER								
34. Global Rating of Positive Formal Thought Disorder The frequency of this rating should reflect the frequency of abnormality and degree to which it affects the patient's ability to communicate.	0	1	2	3	4	5	[17390]	

Other Available Tools for Agitation Assessment

- Agitation in Alzheimer's Screener for Caregivers (AASC)
- Agitated Behavior in Dementia Scale (ABID)
- Pittsburgh Agitation Scale (PAS)
- Revised Memory and Behavior Problems Checklist (RMBPC)
- Agitated Behavior Scale (ABS)

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)

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



Key Learning Points

Agitation

- International Psychogeriatric Association, the consensus definition for agitation in cognitive disorders includes four criteria
- The Cohen-Mansfield Agitation Inventory (CMAI) can be used to assess agitation in AD (rated by a caregiver)
- Agitation in Alzheimer's Disease is highly prevalent across patient settings and disease severity

Psychosis

- Psychosis occurs in the majority of people with Alzheimer's disease over the course of their illness
- The Neuropsychiatric Inventory (NPI) can be used to help assess and rate the severity of psychosis in Alzheimer's Disease
- Psychosis in Alzheimer's Disease is distressing for patients and caregivers and is associated with an accelerated trajectory of decline and dependency

Treatment Approach

Treatment Algorithm

1. **Address safety first:** Take steps to stop harm to self or others and ensure a safe environment, perhaps by moving the person to a safer location
2. **Use in-the-moment interventions to calm and redirect**
3. **Engage the team:** Coordinate a multidisciplinary treatment team
4. **Treat causal factors:** Provide for immediate needs and treat underlying medical or psychiatric symptoms, and remove/adjust environmental triggers
5. **Implement behavioral/nonpharmacologic approaches:** Including direct behavioral plans as well as indirect therapeutic activities
6. **Consider pharmacologic approaches** when symptoms are unresponsive to behavioral approaches, involve active psychiatric illness, or are posing an ongoing risk of harm to self or others
7. **Monitor for response** and re-evaluate/revise assessment findings and treatment approaches

In-the-Moment Behavioral Approaches

- Empathic acknowledgement with active listening
- Nonthreatening body language; adequate space; pleasant facial expression
- Ask what is needed; Offer help or something soothing (eg, a drink or snack)
- Focus on abilities instead of deficits
- When resistant: Assist and don't insist. Give it time. Make it fun
- Engage family and other familial caregivers
- Distract and re-direct
- Use individualized behavioral interventions if known (eg, reinforce positive behaviors and ignore negative ones)

Nonpharmacologic Approaches

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)

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.

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

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. May 11, 2023. Accessed September 2025. <https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-treat-agitation-symptoms-associated-dementia-due-alzheimers-disease>.

Pharmacologic Treatments

Psychotropics Used for Agitation

Medication Class	Pros	Cons	Common Side Effects
Antipsychotics	Best efficacy in studies, although benefits are modest and variable; works for psychosis	<ul style="list-style-type: none"> • Metabolic side effects • Movement disorders • Increased mortality 	<ul style="list-style-type: none"> • Sedation • Cognitive slowing / confusion • Orthostasis • Unsteady gait and falls • Fractures • Extrapyramidal symptoms • Cardio- and cerebrovascular events • Metabolic effects (increased glucose, lipids and prolactin levels)
Benzodiazepines	<ul style="list-style-type: none"> • Works quickly and effectively for calming and sedation • Versatile; as-needed dosing 	<ul style="list-style-type: none"> • Excess sedation and fall risk • Increased confusion • Paradoxical effects 	
Antidepressants	<ul style="list-style-type: none"> • Addresses serotonergic function • Work over time and are generally safe and well-tolerated 	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Poor efficacy in studies • Metabolic effects • Serum levels required 	
Cholinergic Agents	Used to boost cognition	Poor to no efficacy, especially in acute situations	

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
	Brody 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. Brody 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
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

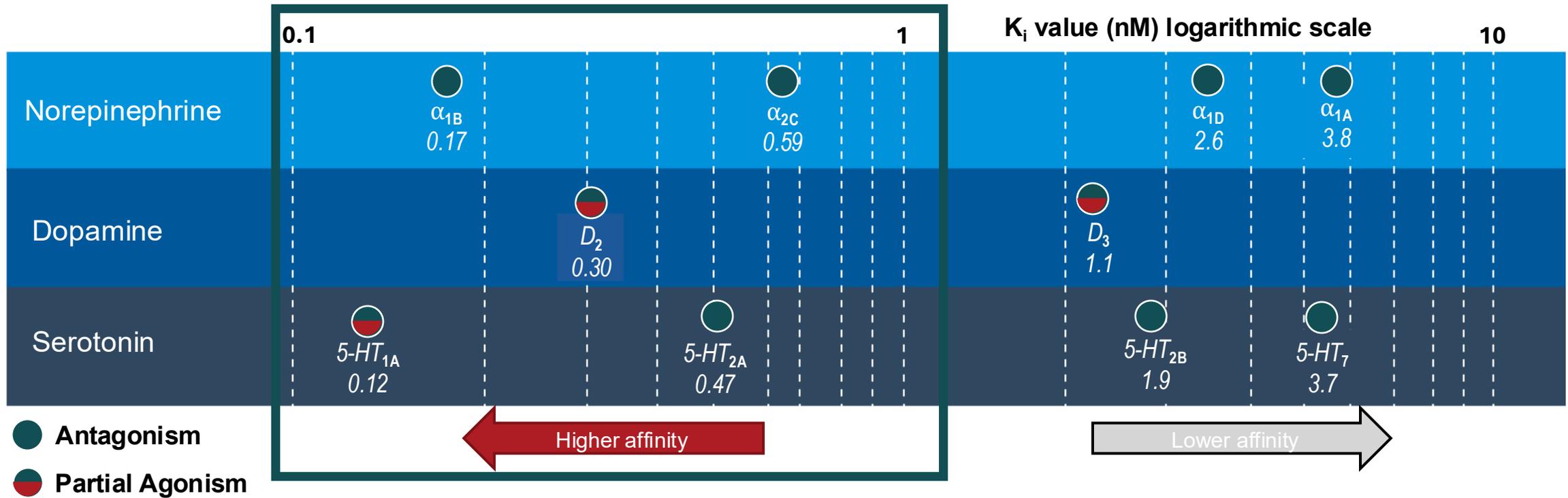
- Tampi et al. point out the basic challenges of antipsychotics: they are frequently used, especially in long-term care, but with limited monitoring, variable efficacy, and moderate to high risk of side effects
- Review of meta-analysis
 - Risperidone, olanzapine, and aripiprazole have modest benefits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

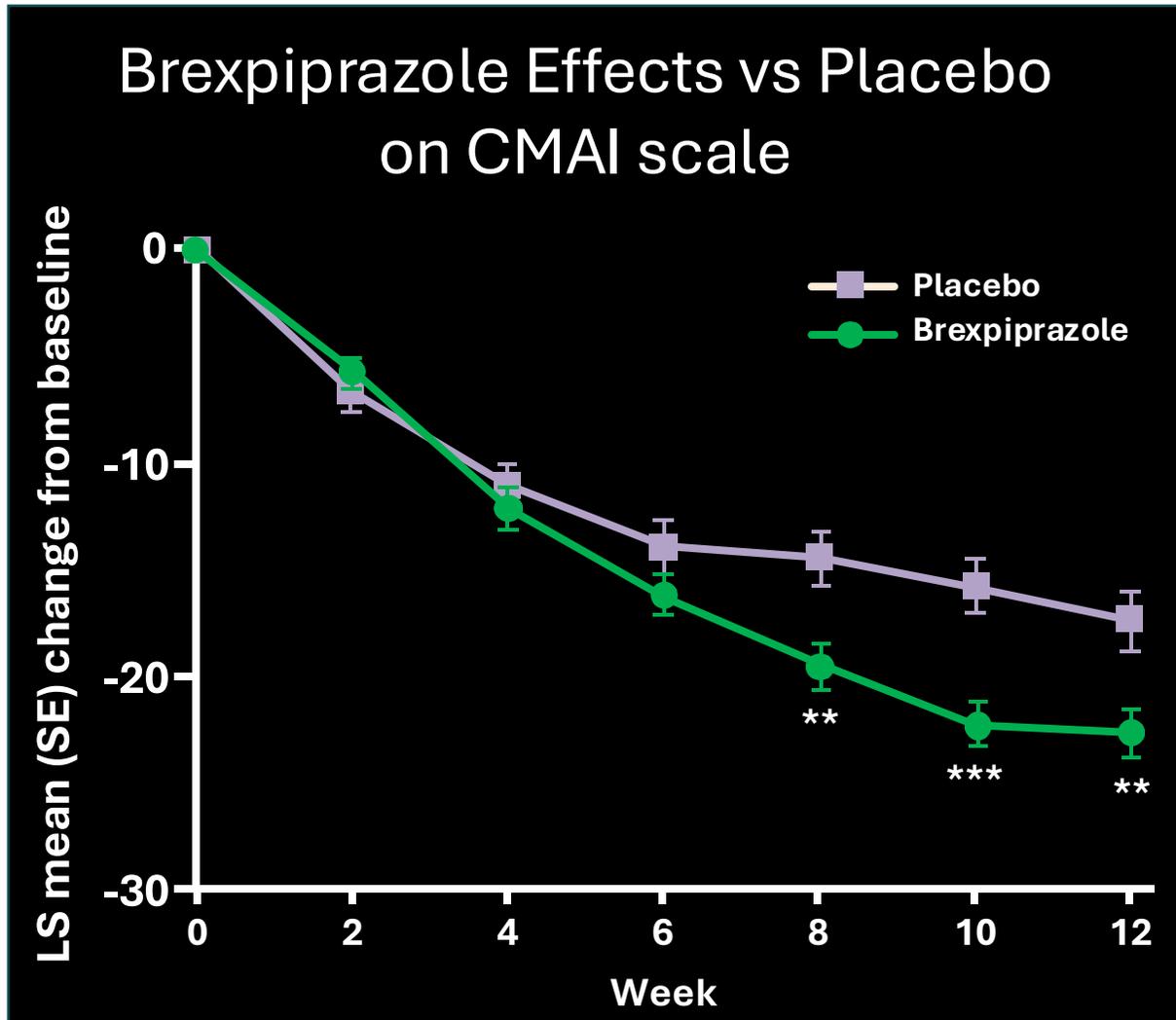
Pharmacologic Rationale for Brexpiprazole as a Potential Treatment for AAD

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



Binding affinity data shown are in-vitro.

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 ($P=.04$)

Atypical Antipsychotics: *Mortality Warning*

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

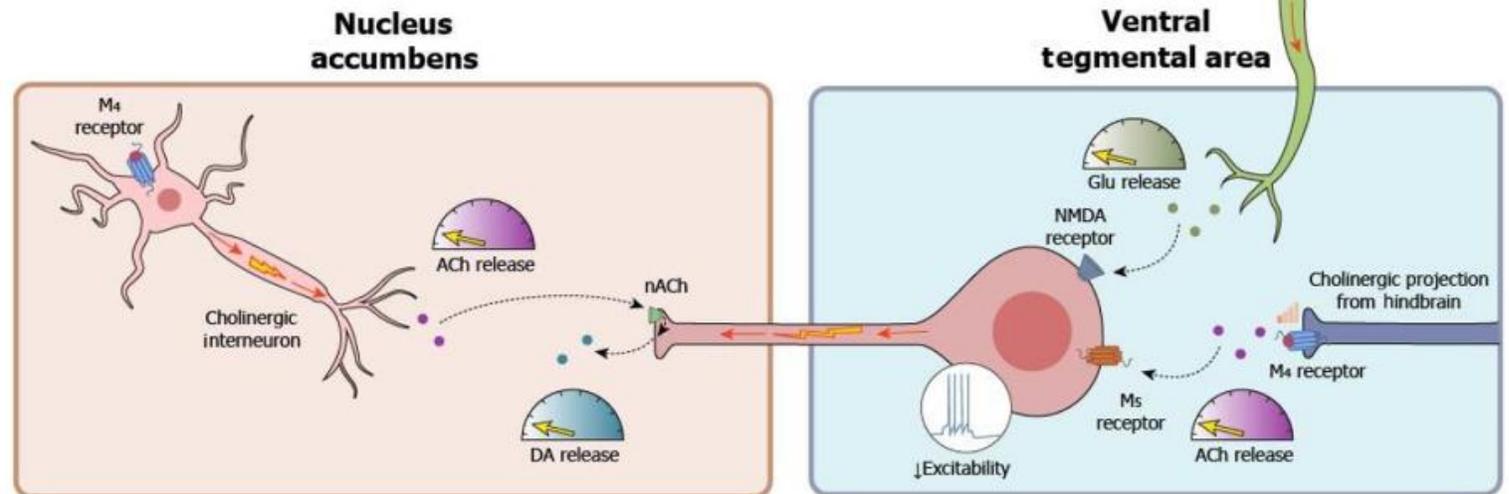
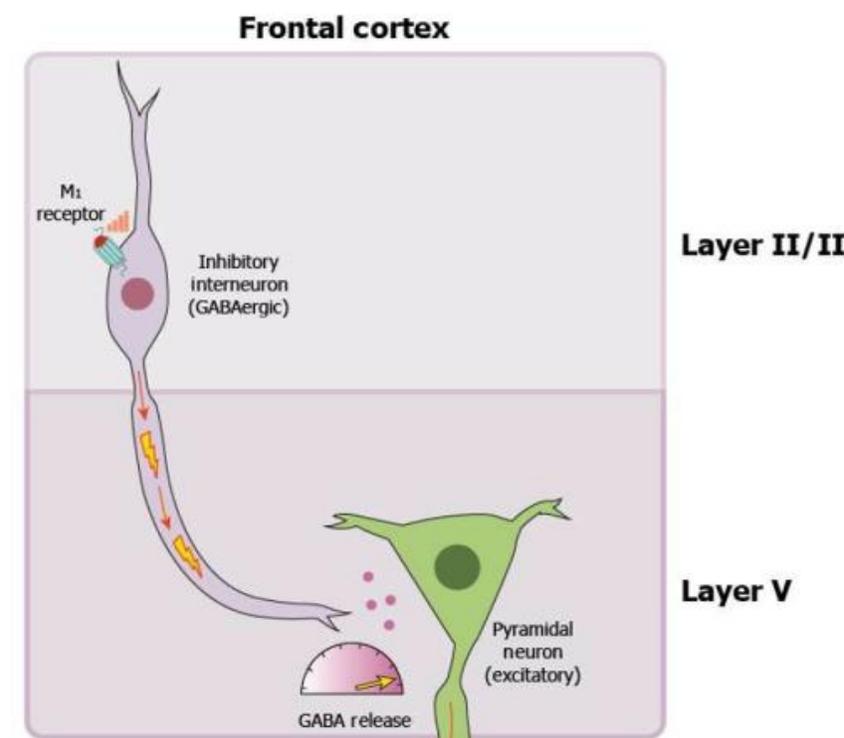
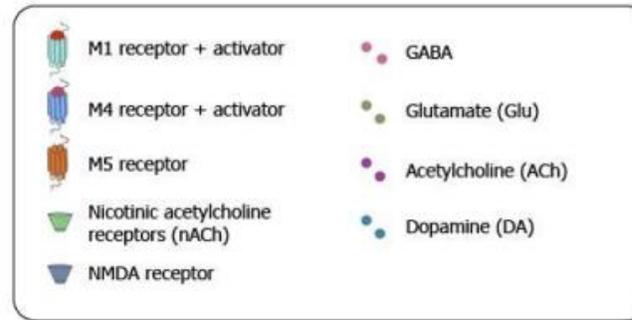
- Listed for elderly patients with dementia-related psychosis
- Analyses of 17 placebo-controlled trials revealed risk of death in drug-treated patients between 1.6 and 1.7x that seen in placebo-treated patients (4.5% vs 2.6%)
- Most deaths were cardiovascular (eg, heart failure, sudden death) or infectious (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

Risk Management with Antipsychotics

- **Off-label usage is permitted** but should be based on scientific support and professional standards of care
- **Documentation** must include a recently-completed comprehensive psychiatric assessment that details the diagnostic assessment with reference to DSM-5 criteria, and provides 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



Triple Mechanism of Action for Antipsychotic Activity of Muscarinic Agonism



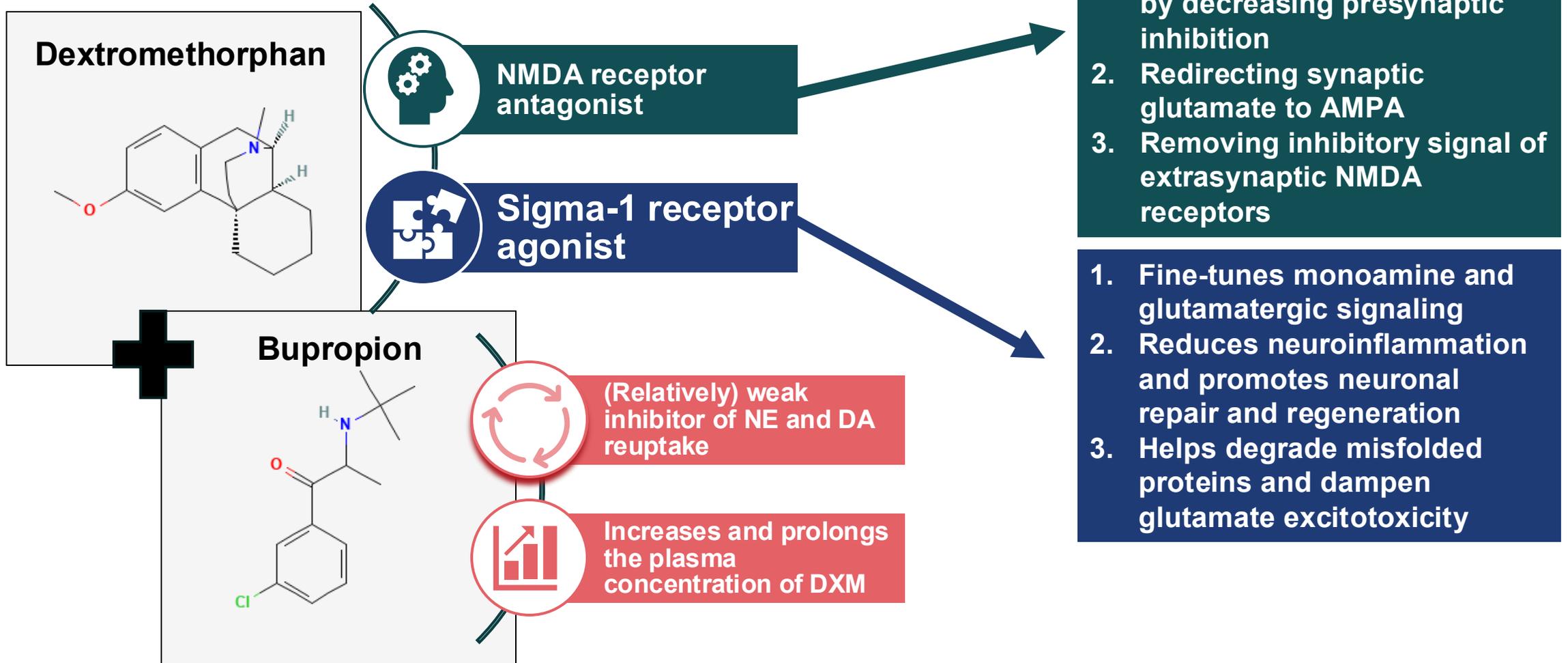
Antidepressants

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's 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.

Dextromethorphan-Bupropion (AXS-05)

Exploring the Key Components



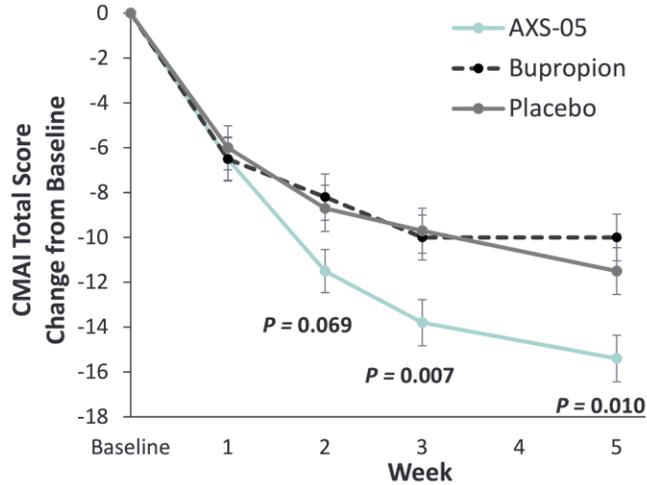
DXM-BUP = dextromethorphan/bupropion; NMDA = N-methyl-D-aspartate; AMPA = α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NE = norepinephrine; DA = dopamine.

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

AXS-05 Phase 3 Clinical Data in AAD



ADVANCE-1: Reduction in CMAI



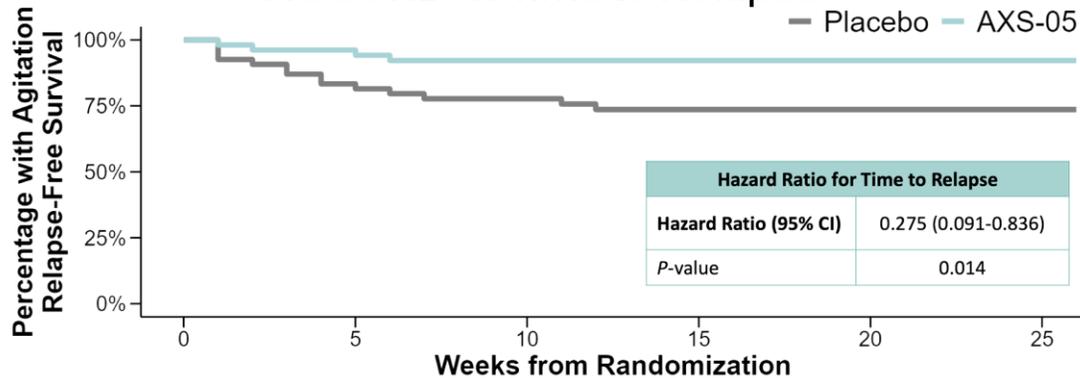
ADVANCE-1
Acute Efficacy Study 5 weeks, N=366
Primary Endpoint: Mean reduction from baseline in CMAI total score at Week 5 AXS-05: 15.4 points placebo: 11.5 points p = 0.010

ADVANCE-2
Acute Efficacy Study 5 weeks, N=408
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

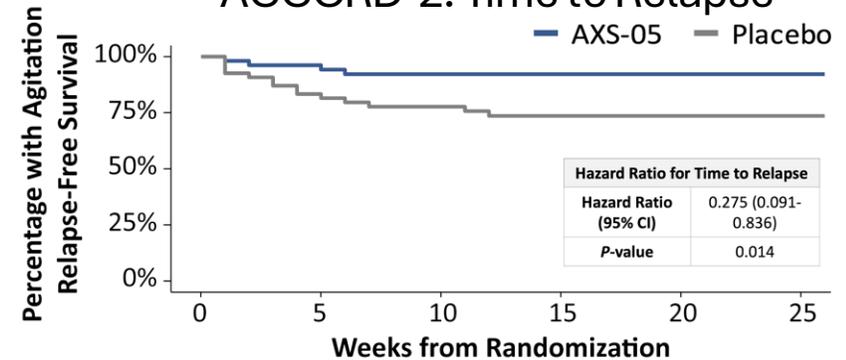
ACCORD-1
Randomized Withdrawal Study Up to 26 wks, N=108
Primary Endpoint: Time to relapse hazard ratio of 0.275; p = 0.014

ACCORD-2
Randomized Withdrawal Study Up to 24 wks, N=167
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: Safety Data and Status

- Most commonly reported adverse events include **dizziness, diarrhea, falls, dry mouth, and somnolence**
- Overall tolerability was favorable with low incidence of serious adverse events, and most adverse events did not require discontinuation of therapy compared with placebo
- The FDA granted breakthrough status in June 2020 to AXS-05 for AAD, and it is being submitted to the FDA in the third quarter 2025 based on data from the four phase 3 studies

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

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	Modest evidence showing behavioral improvement in agitation in one study; clinical trial of deuterated form AVP-786 did not meet endpoints
Dexmedetomidine	α ₂ -adrenergic agonist is a quick-acting sublingual tablet in ~2 hours, with FDA-indication for agitation in schizophrenia and bipolar disorder

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's Disease; October 24-27, 2023. Otsuka. Press Release. February 12, 2024. Accessed September 15, 2025. <https://www.otsuka-us.com/news/otsuka-announces-phase-3-topline-results-avp-786-treatment-agitation-associated-dementia-due>.

Emerging Treatments for Agitation and Psychosis in AD

Target	Asset	Indication	Phase
5-HT _{2B}	Masupirdine	Agitation	Phase III
5-HT _{2A} inverse agonist	ACP-204	Psychosis	Phase II/III
M1/M4 agonist	KarXT (Xanomeline-tropsium)	Psychosis	Phase II
M1/M4 agonist	ML-007C-MA	Psychosis	Phase II
σ1 agonist / NMDA antagonist	AVP-786	Agitation	Discontinued
NMDA antagonist	ASX-05	Agitation	Phase III
α2-adrenergic agonist	Dexmedetomidine	Agitation	Phase II

Nabilone for AAD (Off-Label)

Nabilone is a synthetic oral analogue of THC; it showed significant improvement vs placebo on CMAI in a small 14-week randomized, double-blind crossover trial

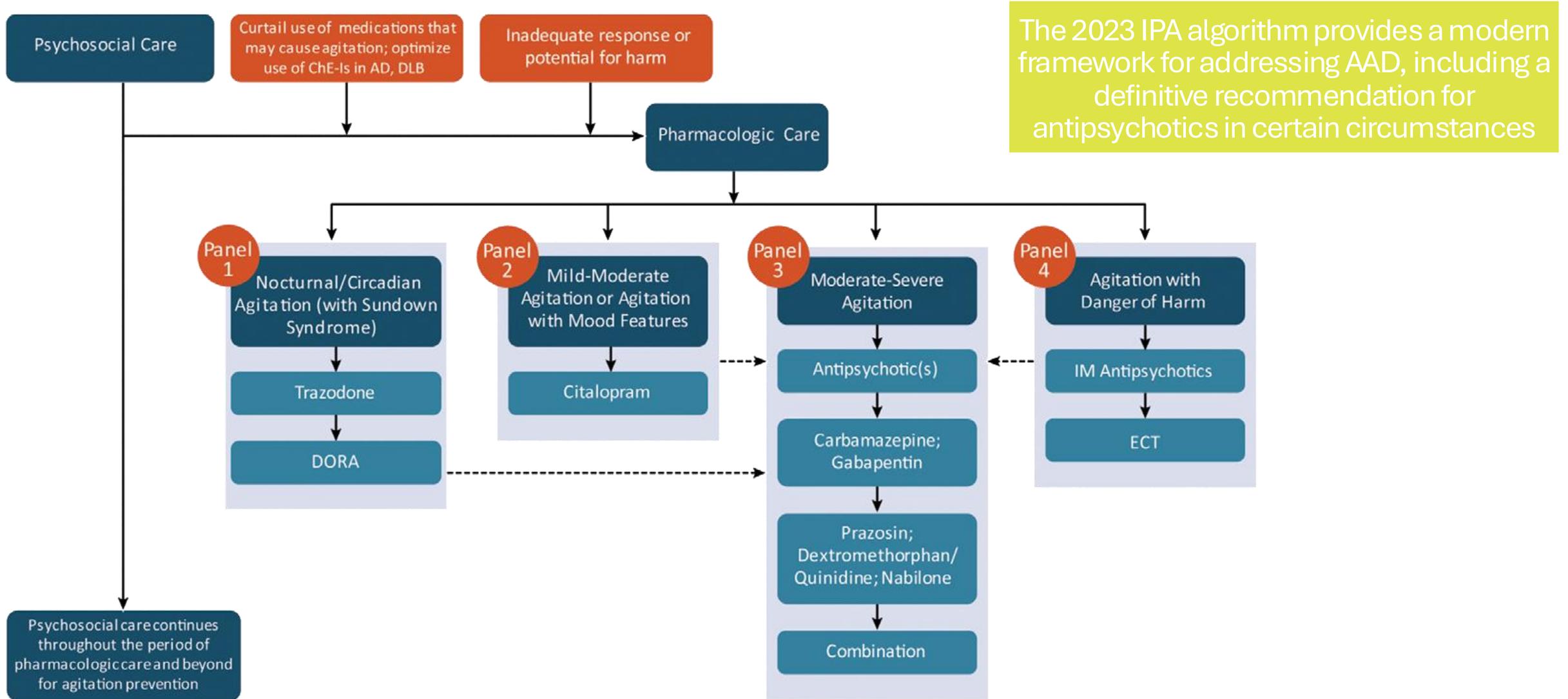
Treatment-Emergent Adverse Events $\geq 5\%$

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

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.

IPA 2023 Algorithm in Alzheimer's



Depression, Apathy, and Anxiety Associated with Dementia

Depression Associated with Dementia

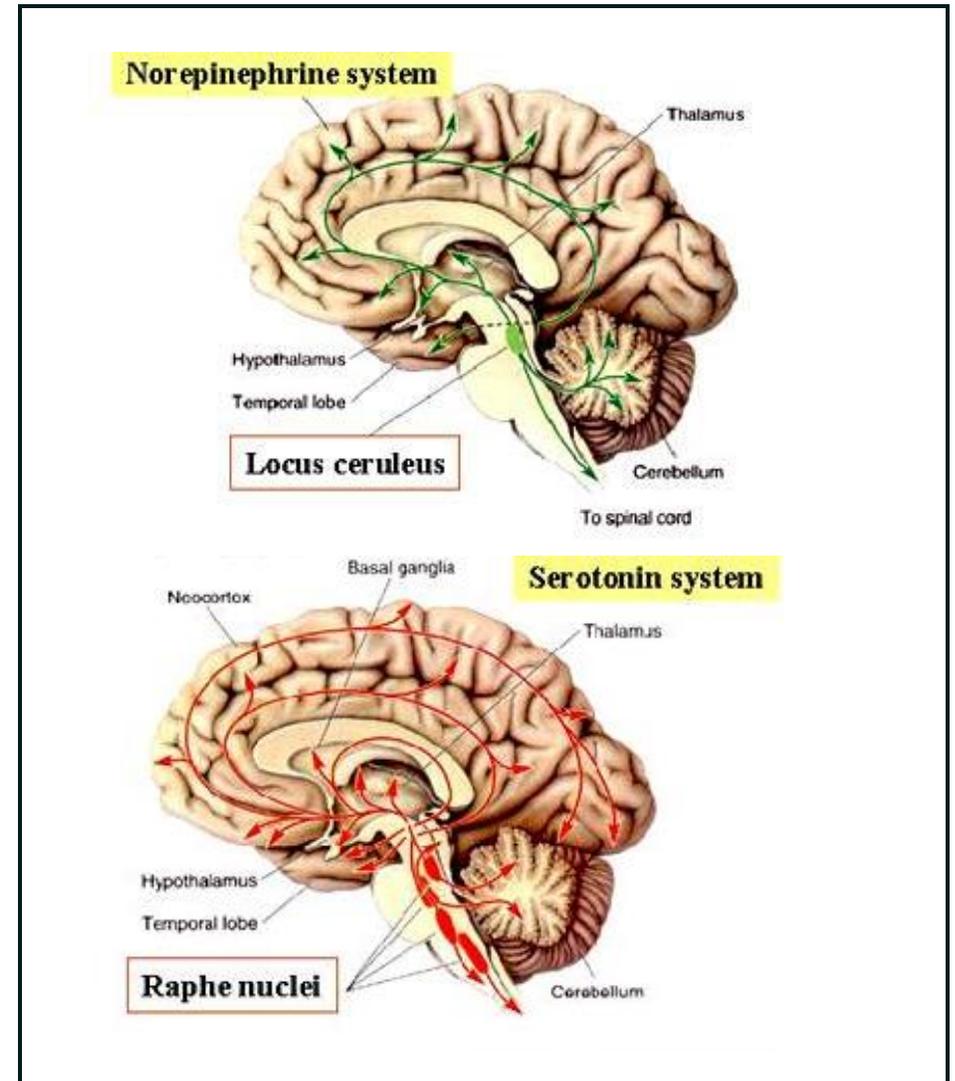
- In general, late-life depression is seen in 9% - 18% of those older than 55 and **accelerates aging** of both body and brain
- Persistent or recurrent lifetime depression is a **risk factor** for all-cause **dementia**
- Antidepressant **response rates** in dementia are **lower**, especially when there is damage to frontal lobe circuits and **executive dysfunction**

The Presentation Is Different

- Verbalizations about deceased relatives, lost abilities, or death
- Irritability, anxiety, pain, somatic complaints, agitation
- Apathy, isolative behaviors
- Noncompliance with treatment; slow or poor progress in rehab
- Failure to thrive
- Indirect life-threatening behaviors

Similar Causes for Depression and Dementia

- Hypothalamic-pituitary-adrenal (HPA) axis dysfunction
- Brain atrophy (especially in hippocampus and prefrontal cortex)
- Neurocognitive decline related to beta-amyloid and tau deposition
- Neuroinflammation
- Degeneration of key nuclei: locus ceruleus (norepinephrine) and raphe nucleus (serotonin)



Vascular Depression

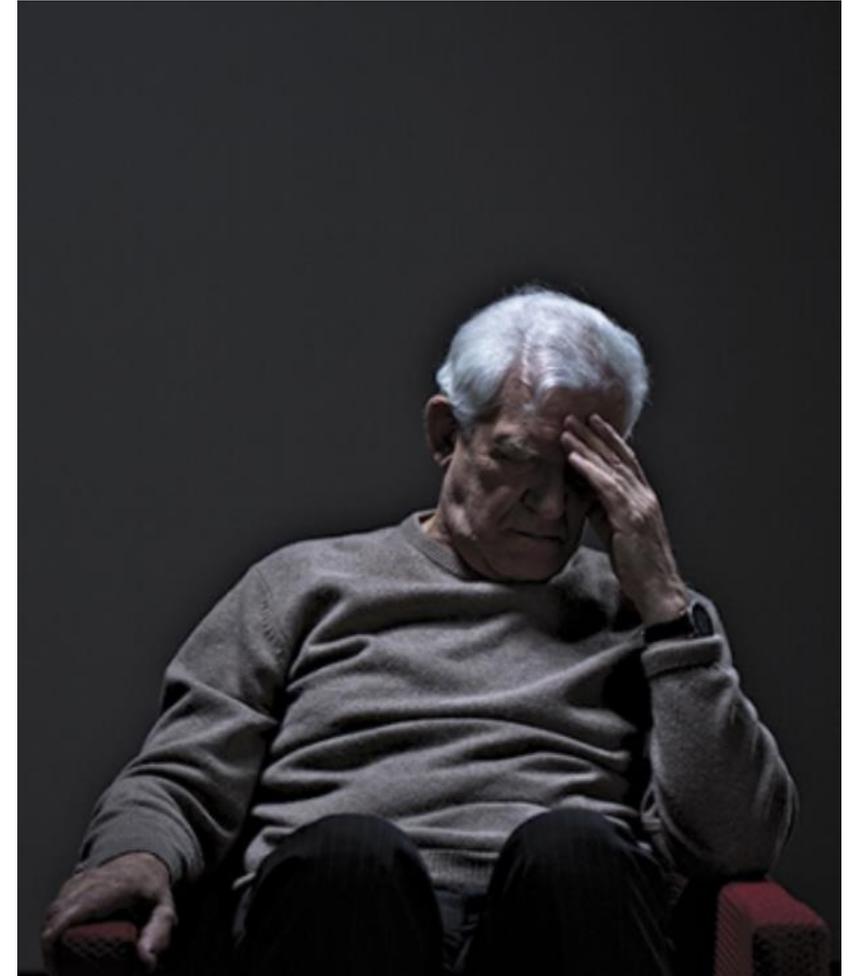
- Vascular depression is defined by a depression associated with cerebrovascular disease, either small vessel ischemic disease or stroke
- Depression is highly associated with subcortical VaD and is a core symptom of CADASIL (*cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy*)
- Post-stroke depression is associated with poorer recovery, more cognitive deficits, lower quality of life, and increased mortality, compared to stroke alone

SYMPTOMS

- Cognitive impairment and slowing
- Executive dysfunction
- Psychomotor retardation
- Apathy
- Gait disturbances
- Parkinsonism

Treatment of Depression Due to Dementia

- Antidepressant treatment has shown limited efficacy
- Modify nonpharmacologic factors including pain, neuropsychiatric symptoms, cognitive decline, social isolation, and quality of life
- Physical exercise improves release of BDNF and decreases beta-amyloid and tau formation
- Therapeutic activities like music and horticultural therapy may help
- Psychotherapeutic modalities might help, such as cognitive-behavioral therapy and compassion-based therapy



BDNF = brain-derived neurotrophic factor.

Lenouvel E, et al. *Psychiatry Res.* 2024;340:116114. El Baou C, et al. *Geriatr Nurs.* 2024;20(12):8844-8854. Craig C, et al. *Int J Geriatr Psych.* 2018;33(12):1727-1735. Dudas R, et al. *Cochrane Database Syst Rev.* 2018;8(8):CD003944. Orgeta V, et al. *Cochrane Database Syst Rev.* 2022;4(4):CD009125.

Anxiety Associated with Dementia

- Anxiety disorders are common conditions in life, seen in roughly 8% of older adults (ranging from 1.2% to 28% depending on the disorder), with GAD and phobias being most common
- Symptomatic anxiety and anxiety disorder have higher rates associated with Alzheimer's disease (AD) and other dementias, depression, COPD, and Parkinson's disease
- They are associated with other neuropsychiatric symptoms such as depression or agitation
- There is no established association between anxiety and amyloid or tau deposition, although PTSD is considered a potential risk factor for AD

COPD = chronic obstructive pulmonary disease; GAD = generalized anxiety disorder; PTSD = posttraumatic stress disorder.

Crocco EA, et al. *Curr Treat Options Psychiatry*. 2017;4(1):33-46. Bryant C, et al. *J Affect Disord*. 2008;109:233-250. Livingston G, et al. *Lancet*. 2024;404(10452):572-628.

What About Benzodiazepines? To Use or Not

To USE

- They work quickly and are effective
- At low doses there is little risk of dose escalation or addiction
- Low risk of drug: drug interactions except with ETOH or other sedative-hypnotics
- The purported risk of dementia is not well supported



To NOT USE

- Concerning risk to benefit ratio
- Prescribed by non-specialists
- Increased risks of
 - Falls with fractures (20% - 50%)
 - Excess sedation
 - Cognitive deficits
 - MVAs
 - Overall mortality (1.2 – 3.7x higher rate)

ETOH = ethanol/ethyl alcohol.

Otto MA. Clin Psychiatry News. July 9, 2019. Accessed September 2025. <https://www.mdedge.com/fedprac/article/204322/anxiety-disorders/misguided-fear-keeping-benzodiazepines-elderly>. Salzman C, Shader R. *J Clin Psychopharmacol*. 2015;35(1):1-3. Markota M, et al. *Mayo Clin Proc*. 2016;91(11):1632-1639. Hill KD, Wee R. *Drugs Aging*. 2012;29(1):15-30.

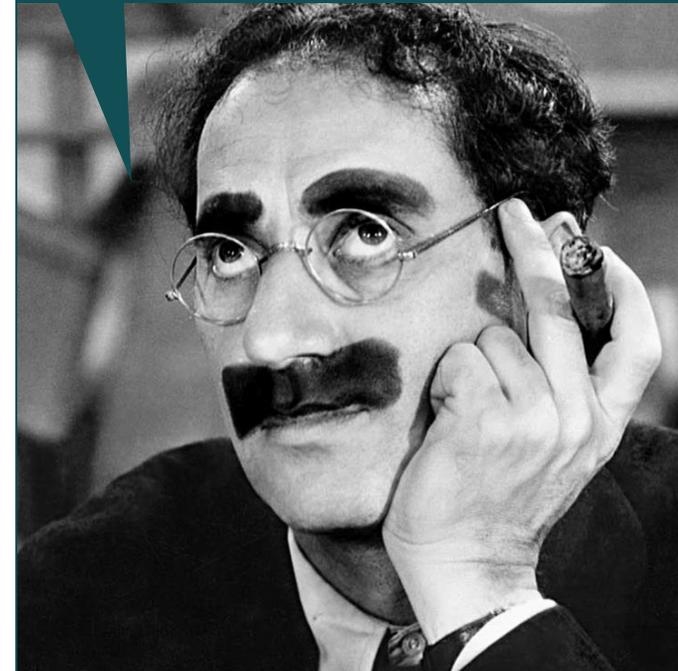
Pharmacologic Agents for Anxiety Disorders

- **Buspirone:** It has shown some efficacy in GAD in adults but not elderly; as well as some efficacy for anxiety / agitation in dementia
- **Tricyclic antidepressants:** Once the gold standard and efficacious for anxiety disorders, they have problematic side effects in the elderly (orthostasis, anticholinergic effects, sedation)
- **Antipsychotics:** Quetiapine is often used for symptomatic anxiety and anxiety disorders, and has shown efficacy in the treatment of GAD
- **Mood Stabilizers:** No strong data supporting any mood stabilizer for anxiety disorders, except for PTSD
- **Beta-Blockers:** Not recommended due to lack of evidence and risk of side effects and drug:drug interactions

What Is Apathy?

- Apathy is a fundamental problem of **motivation**, manifested in behavior, cognition, and emotional expression. It is **not** a mood disorder and does not imply underlying depression
- Apathy is the most common behavioral problem in dementia
- Apathy is seen in 60%-90% of patients with Alzheimer's disease
- Apathy interferes with patient compliance and degree of participation in treatment

**I Don't Give a
DAMN about
apathy!** – Groucho Marx



Treatment of Apathy

Reviews over 50 studies of apathy in multiple dementia types have shown

- Overall limited efficacy for the stimulant methylphenidate and less evidence for modafinil
- Variable to poor efficacy for antidepressants (citalopram, bupropion), cognitive enhancers (rivastigmine, donepezil, galantamine, memantine), antipsychotics (olanzapine), valproate, and ginkgo biloba
- Exercise has shown reasonable efficacy



Key Learning Points

- Up to 80–90% of patients with Alzheimer's disease experience neuropsychiatric symptoms (NPS), which worsen outcomes and increase caregiver burden
- NPS reflect dysregulation across serotonin, norepinephrine, dopamine, and glutamate systems, creating an imbalance between emotional drive and executive control
- Standardized assessments such as the CMAI (for agitation) and NPI (for psychosis) help quantify symptoms and guide management
- The DICE model - Describe, Investigate, Create, Evaluate - supports systematic assessment and multidisciplinary care
- Both nonpharmacologic (behavioral, sensory, structured activities) and pharmacologic strategies (e.g., brexpiprazole, AXS-05, KarXT) are essential for effective symptom control
- Optimal outcomes depend on interdisciplinary teamwork and active caregiver involvement in identifying and managing NPS