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Agitation, Psychosis, and Other Behavioral Symptoms in Alzheimer's Disease

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Learning Objectives

- Employ evidence-based tools for the assessment of behavioral symptoms in patients with AD
- Identify the hypothesized mechanism of disease contributing to behavioral symptoms, including neurotransmitter and brain region involvement
- Assess the latest clinical evidence for new and emerging options for the treatment of behavioral symptoms in AD

New Treatments for Early AD: Lecanemab and Donanemab

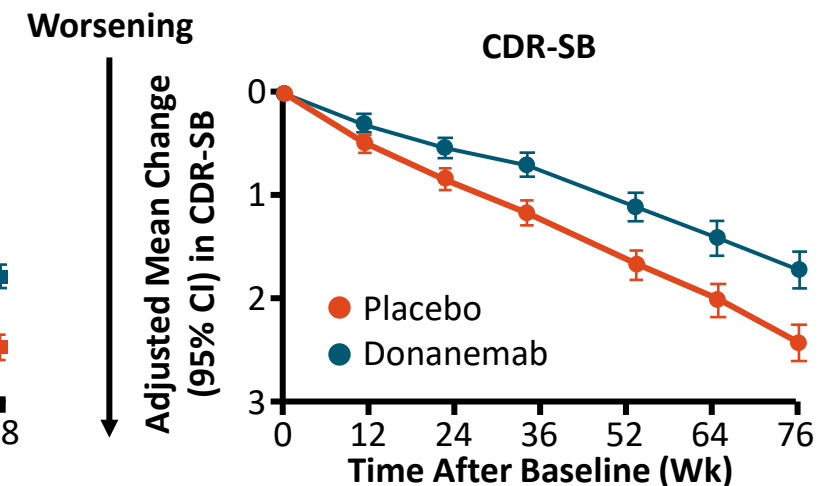
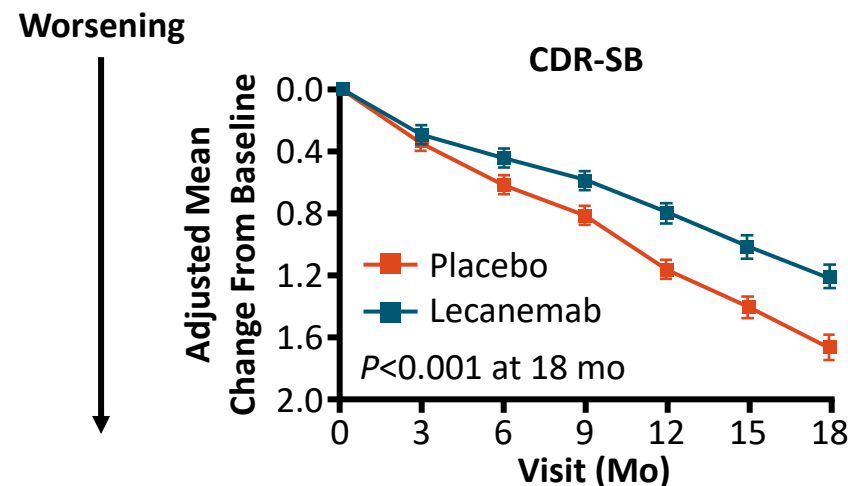
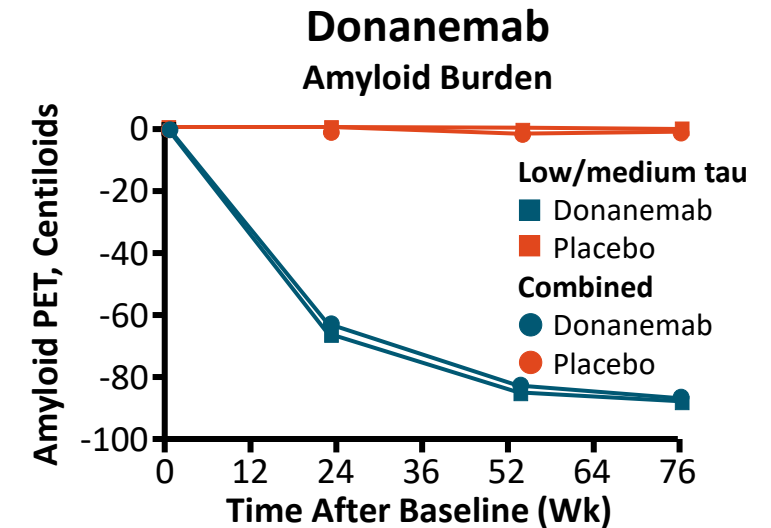
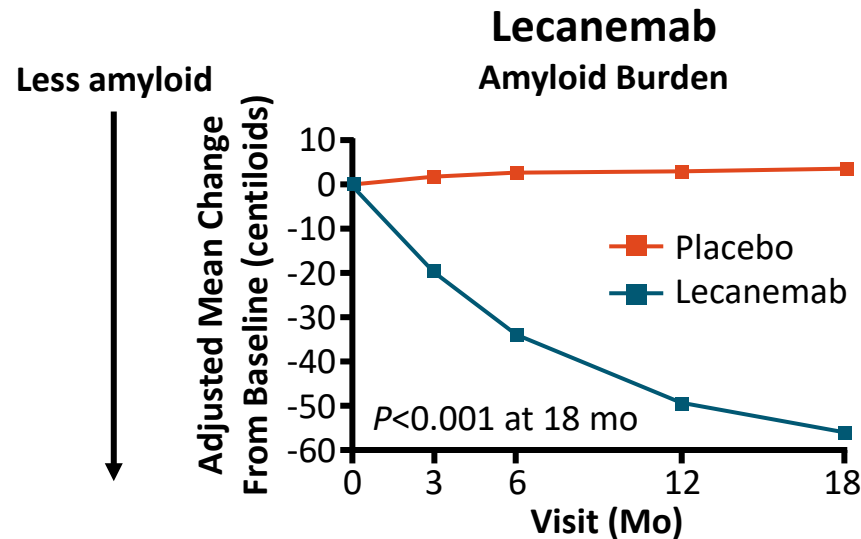
- Anti-amyloid mAbs
FDA-approved for early AD

- Elevated CNS amyloid
- MCI or mild dementia

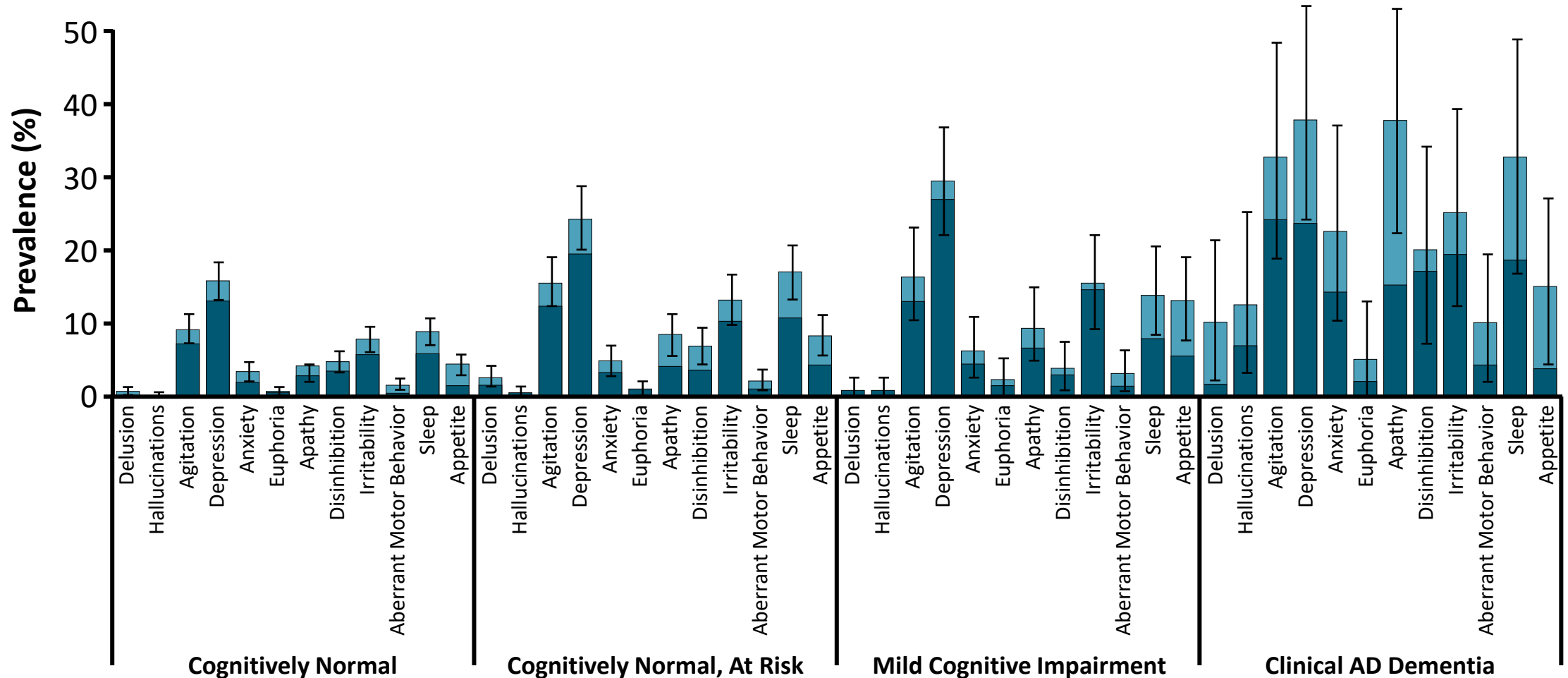
- 2023 Appropriate Use Recommendations

- Risk

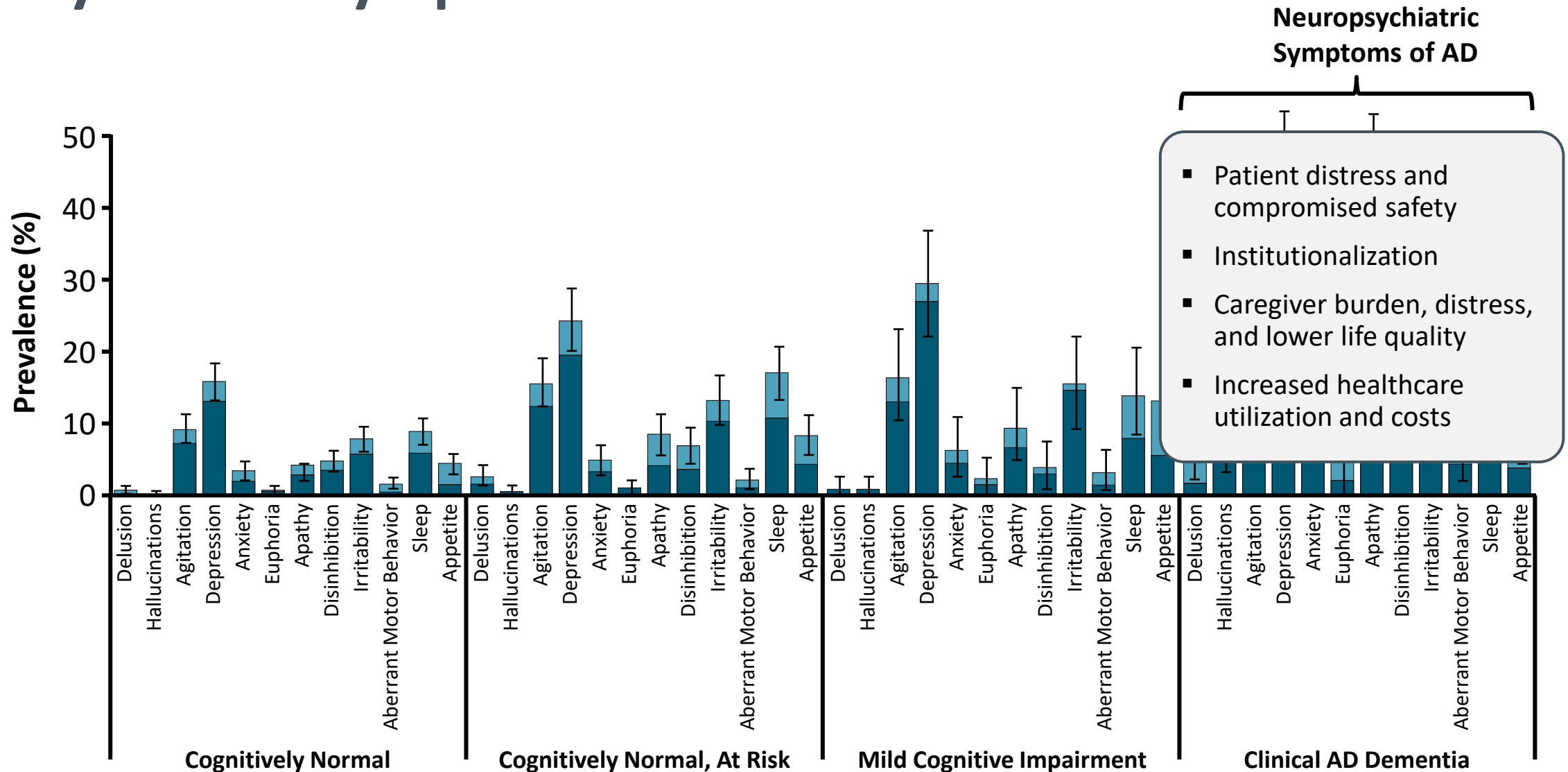
- ARIA-E and -H
- Risk increased by *APOE 4/4* or anticoagulants



Psychiatric Symptoms and AD

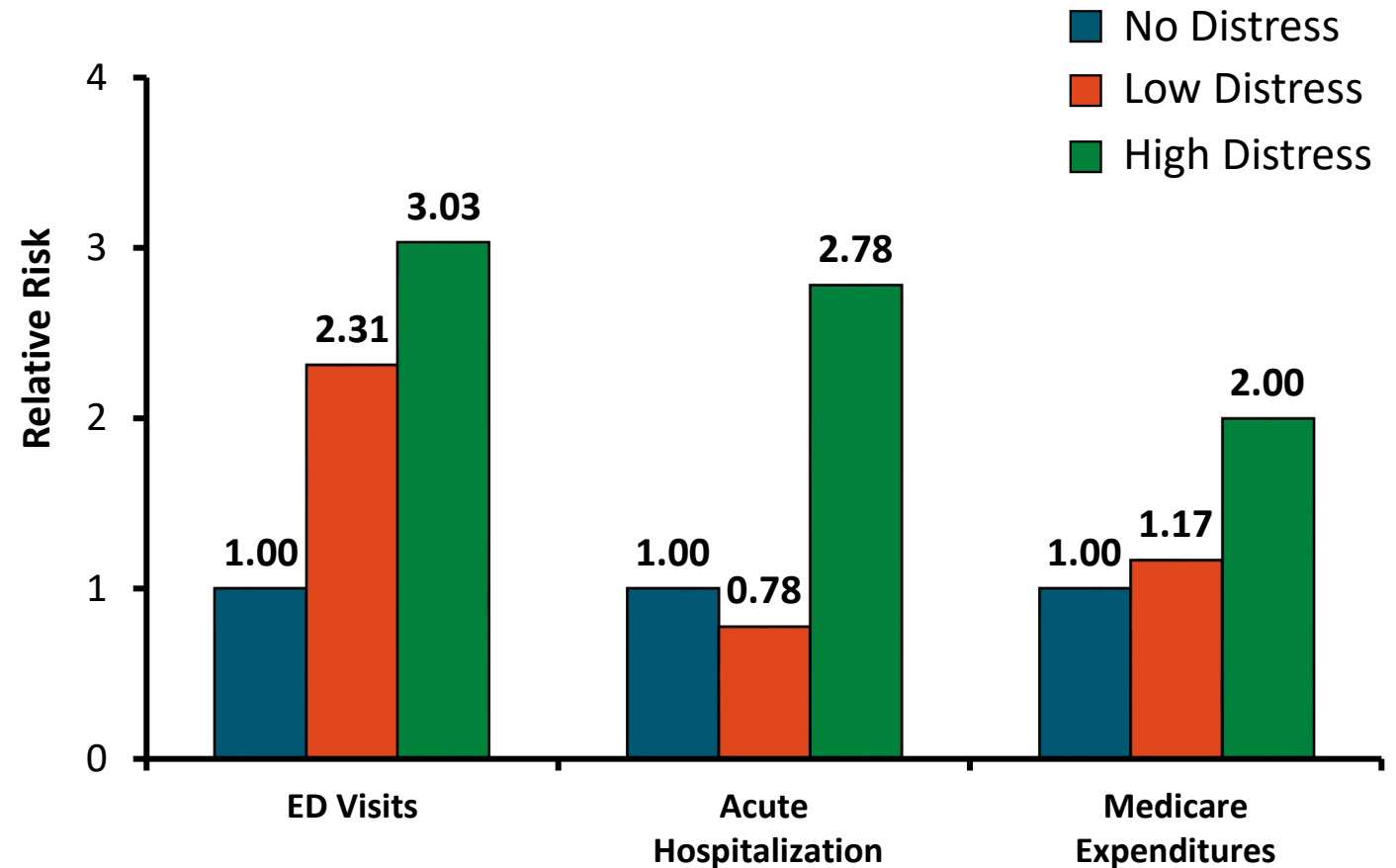


Psychiatric Symptoms and AD



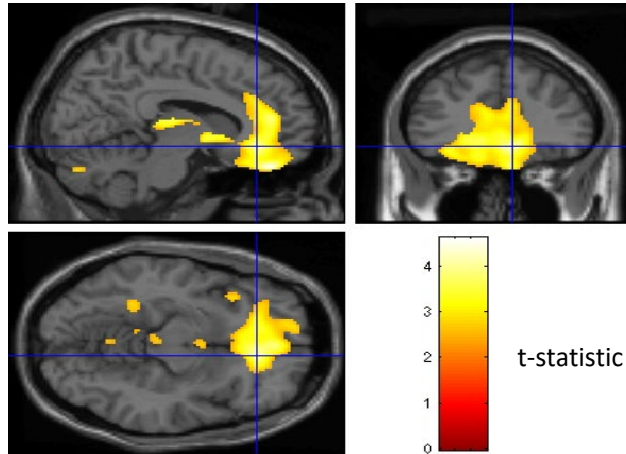
Neuropsychiatric Symptoms: Consequences

- Patient distress and compromised safety
- Recurrence
- Institutionalization
- Caregiver burden, distress, and lower life quality
- Increased healthcare utilization and costs

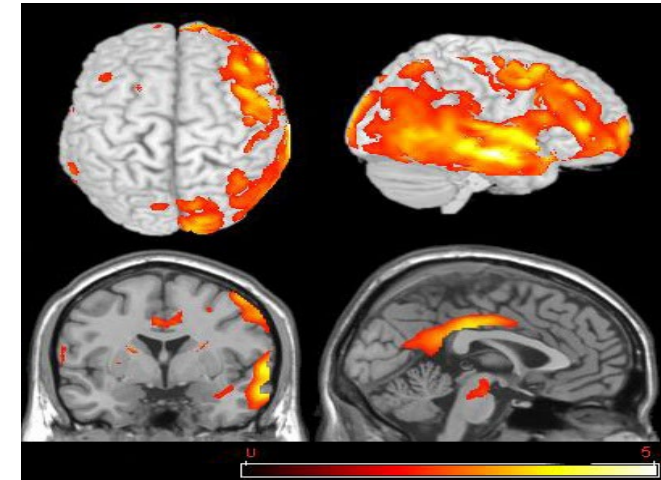


Neurobiology of Psychiatric Symptoms in AD

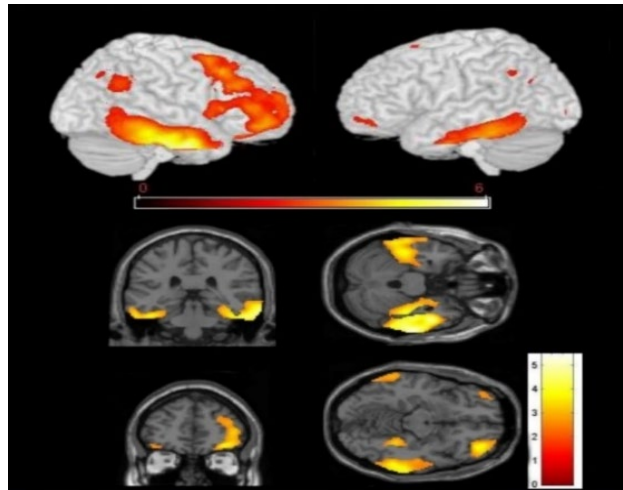
■ Apathy



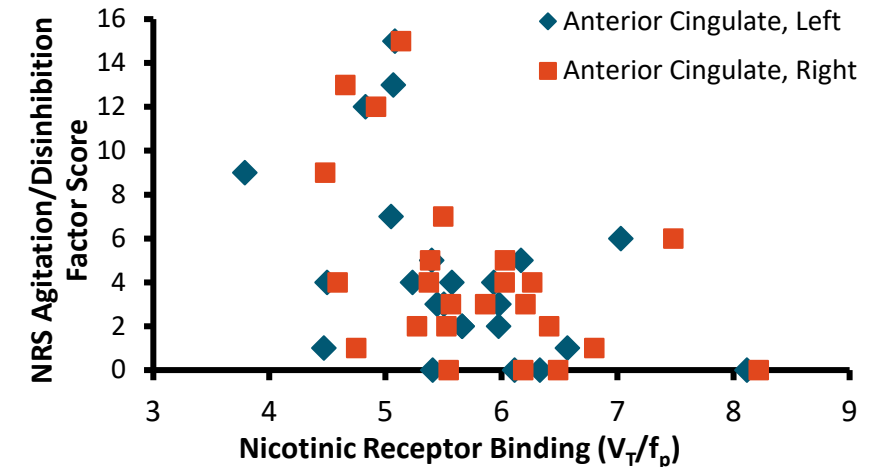
■ Hostile agitation



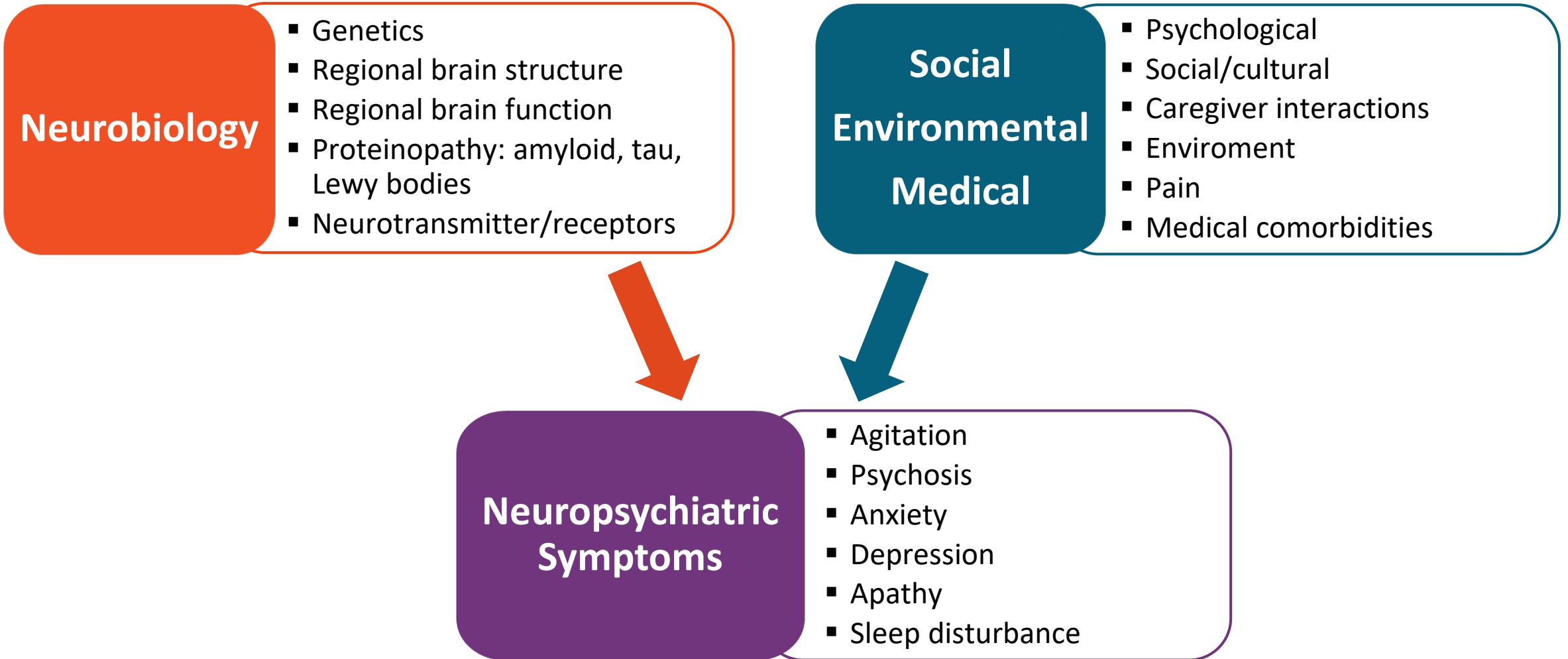
■ Delusions



■ Agitation and brain cholinergic systems



Neuropsychiatric Symptoms in Dementia



Agitated Behaviors in AD

Definition

- Heterogeneous behaviors
 - Physical aggression
 - Verbal aggression
 - Excessive motor activity
- Related to anxiety, fear, irritability, impulsivity

Prevalence

- Agitation: 20%-70%
- Physical aggression: 10%-25%
- Psychosis: 20%-40%

Associated With

- Premorbid aggression
- Rapid cognitive decline
- More frequent falls
- Increased mortality

Addressing Agitated Behaviors

What's the behavior?

- Talk with patient and carers
- Context and spectrum of behaviors

Are there “medical” causes?

- Pain, delirium, medications, sensory deficits

Are there other contributors?

- Boredom, communication, misinterpretation, environment, anxiety, psychosis

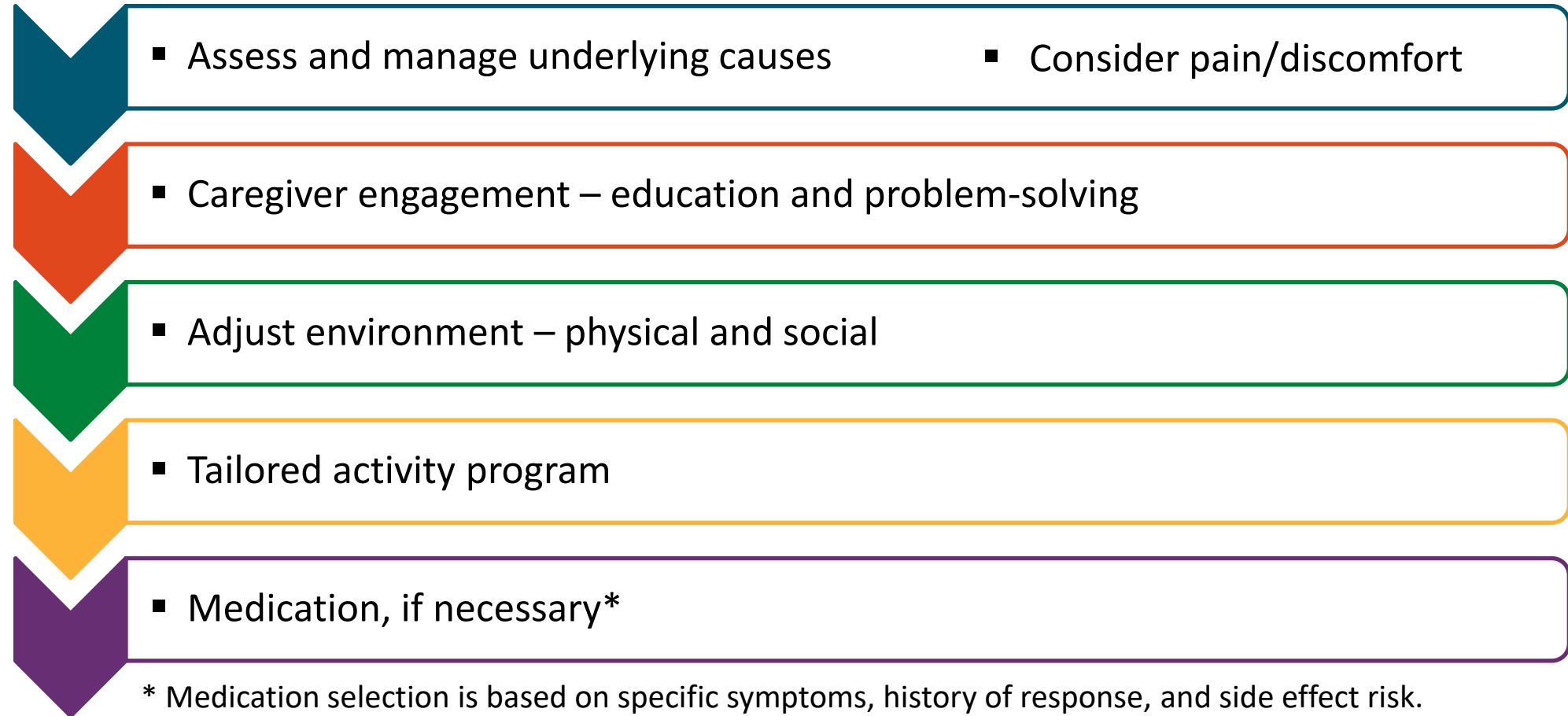
What's the acute risk?

- Safety measures

Personalized interventions: Caregivers

- Education
- Problem-solving
- Support

A Patient-Centered Approach to Agitated/Aggressive Behavior in AD



Psychosocial Interventions

1 Caregiver

- **Problem-solving:** avoiding triggers, routines, reassurance, distraction, managing affect, let it go
- **Emotion-focused:** support, time for themselves
- **Education:** link to neurocognitive disorder
- Address stress and depression
- Respite care
- Support groups

2 Patient

- Repetition, redirection, reassurance
- Improve communication, pleasant activities, social engagement

3 Environment

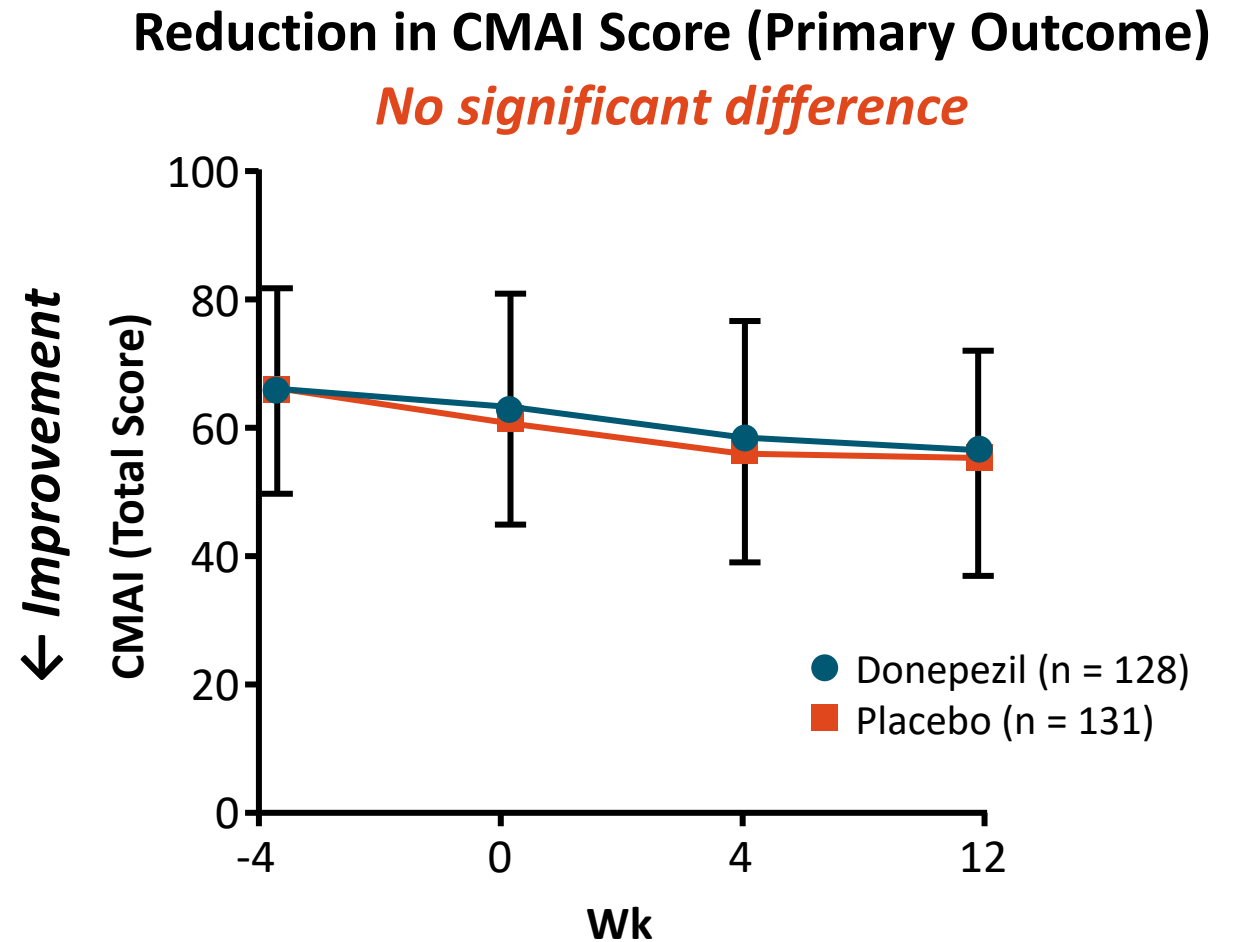
- Optimal stimulation, wandering paths, visual barriers

Current Evidence Gaps

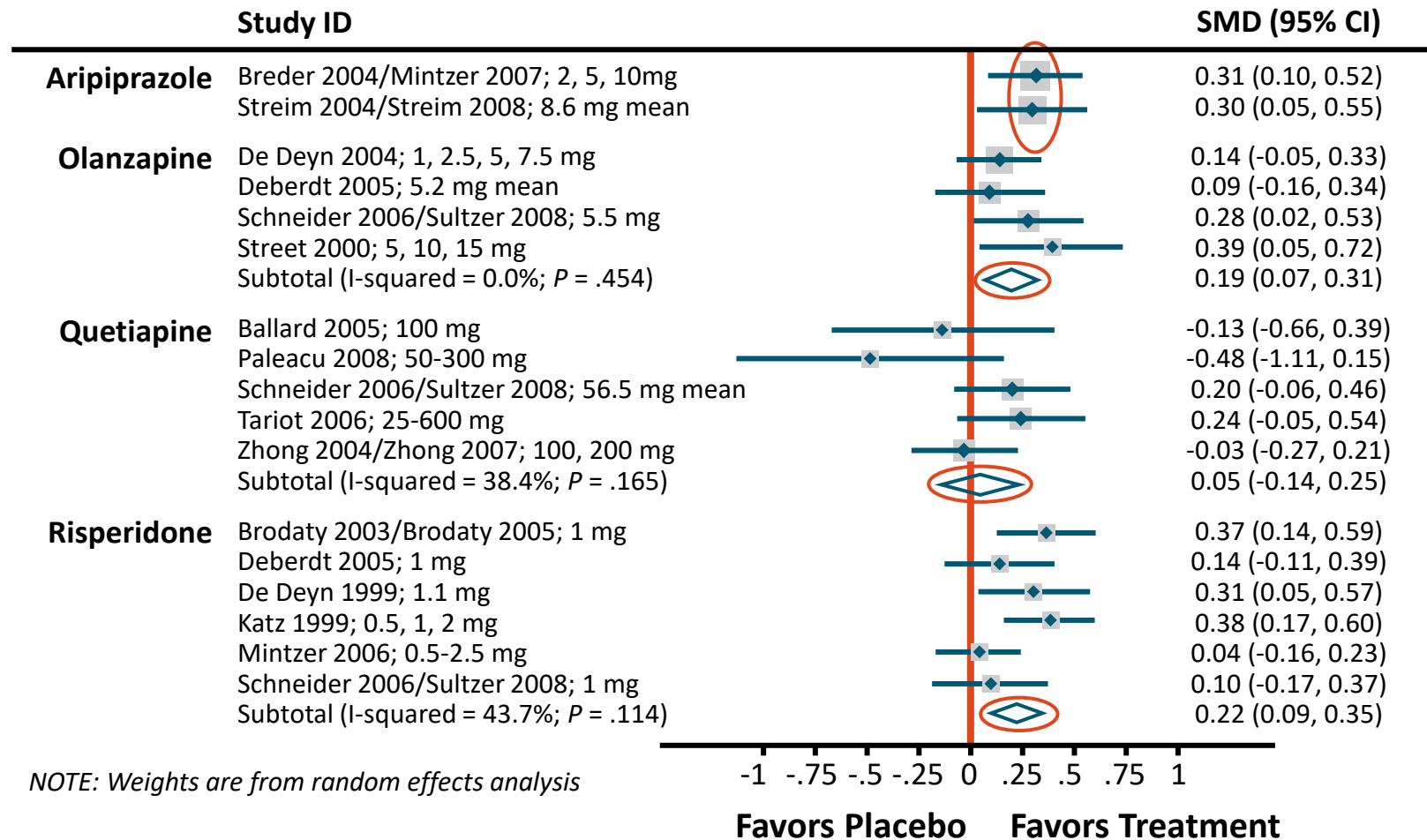
- Severe symptoms, specific symptoms that best respond, implementation strategies
- How best to integrate psychosocial interventions and pharmacotherapy

Cholinesterase Inhibitors for Agitation in AD: CALM-AD

- 272 patients with AD and agitation
- 12-wk trial
- Donepezil 10 mg/day vs placebo



Atypical Antipsychotic Efficacy for Agitation in AD



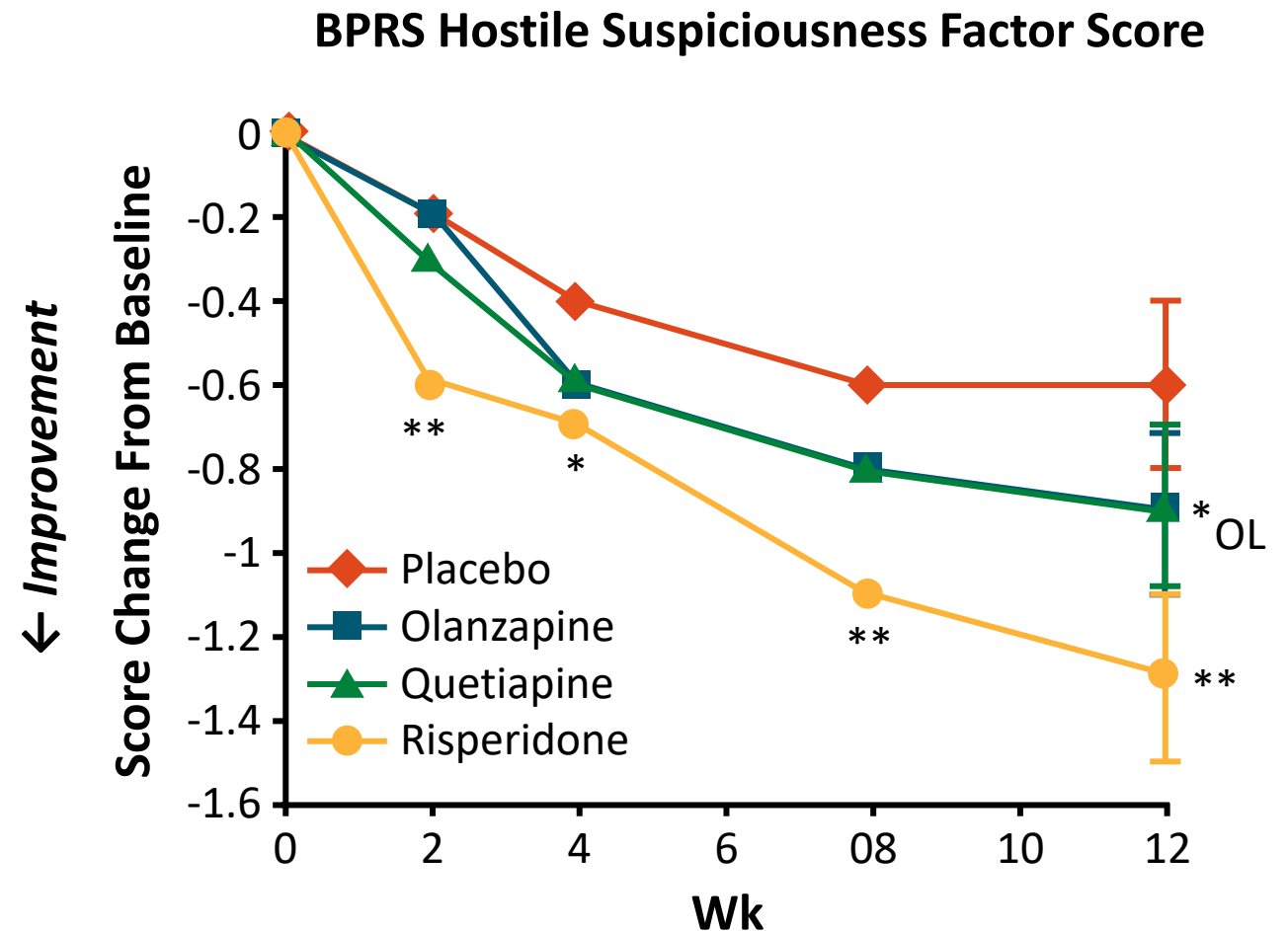
Overall effect sizes:

← **Agitation: 0.20**

- Psychosis: 0.11
- Total behavioral symptoms: 0.16

Hostile Suspiciousness Factor Score: CATIE-AD

- Hostility, suspiciousness, uncooperativeness
- Symptoms improved by 30% (pooled active treatments)
- Greatest improvement among behavioral measures



Adverse Events With Antipsychotics

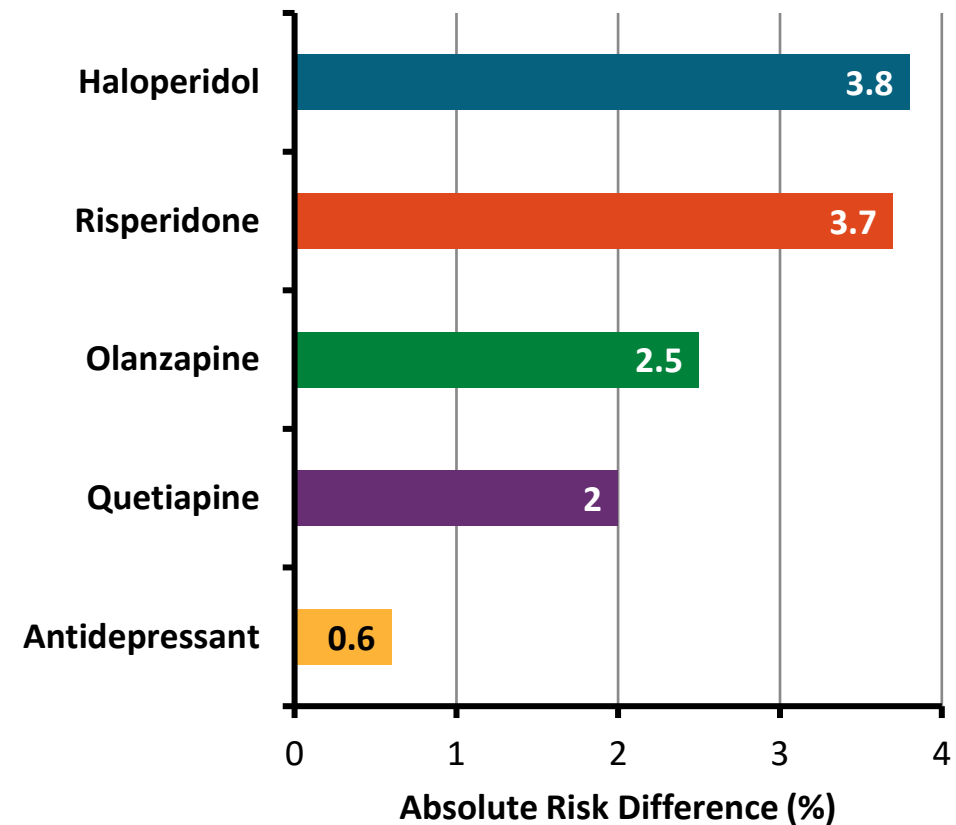
Commonly include:

- Somnolence
- Extrapyrarnidal effects
- Gait difficulty
- Edema
- Urinary symptoms
- Metabolic syndrome/weight gain
- Cognitive decline
- Cerebrovascular events
- Mortality

Clinicians usually avoid:

- Haloperidol → if parkinsonism
- Risperidone → if cerebrovascular disease or parkinsonism
- Olanzapine → if parkinsonism or metabolic or sedation concerns
- Quetiapine or aripiprazole → if metabolic concerns

Adjusted Absolute Mortality Risk: User vs Matched Nonuser



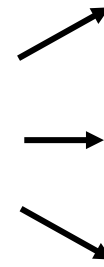
Antipsychotic Discontinuation in AD (ADAD)

PHASE A
Open Treatment
16 Wk

Risperidone
0.25-3 mg/d
N = 180



110 Responders
Randomized
Mean dose:
0.97 mg/d



PHASE B

16 Wk

Randomized

16 Wk

Risperidone continued

Risperidone continued

Risperidone continued

Placebo

Placebo

Placebo

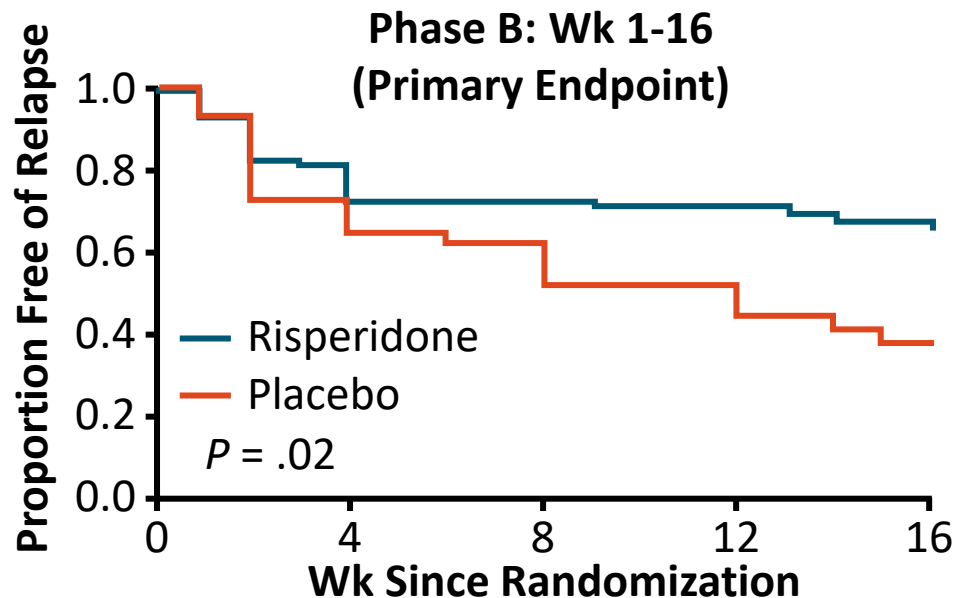
Relapses:

Risperidone: 33%
Placebo: 60%

Risperidone: 15%
Placebo: 48%

No substantial difference in AEs

Among those with known behavioral symptoms that responded to initial risperidone treatment, the relapse rate was **60% when crossed over to placebo** vs **33% when continued on risperidone** for 4 mo



Brexpiprazole for Agitated/Aggressive Behavior in AD

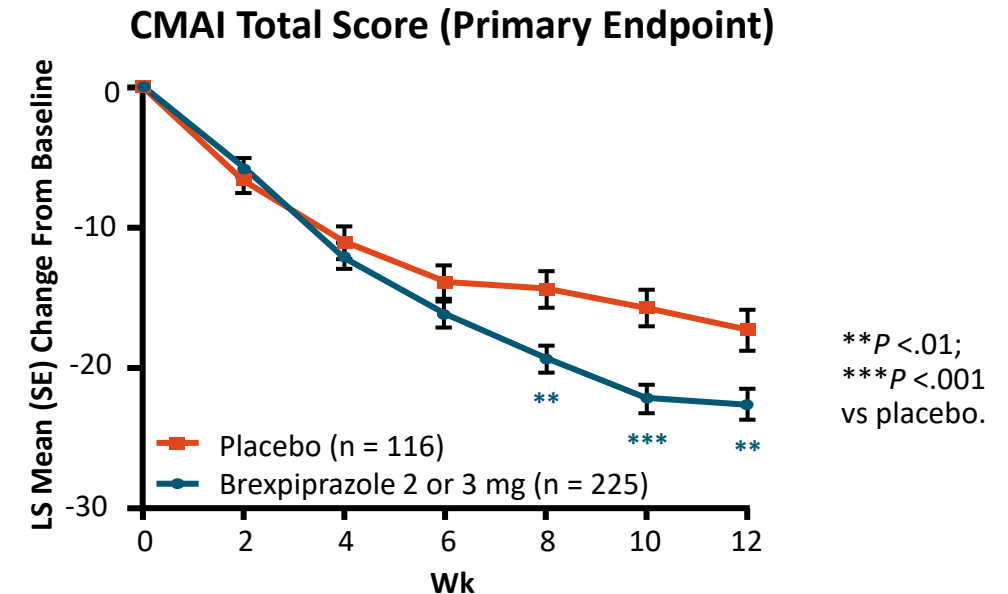
- Multiple receptor effects:
 - Partial agonist: 5-HT_{1A}, D₂
 - Antagonist: 5-HT_{2A}, α_{1B} , α_{2C}
- Previously approved as treatment for schizophrenia and adjunctive therapy for major depression
- 3 trials completed in patients with predominantly “moderate” dementia (MMSE 13-18)

Trial	Sample Size	Participants	Mean Age	Mean Baseline CMAI Score	Dose (QD)*	Treatment Duration
283 ¹	433	63% care facility	74	71	1 or 2 mg/d	12 wk
284 ¹	270	55% care facility	74	71	Flex dose: 0.5-2 mg/d	12 wk
213 ²	345	43% care facility	74	80	2 mg, 3 mg/d	12 wk

*Dose titrated over 2-4 wk (3-4 wk for 2-mg dose).

Brexpiprazole for Agitated/Aggressive Behavior in AD

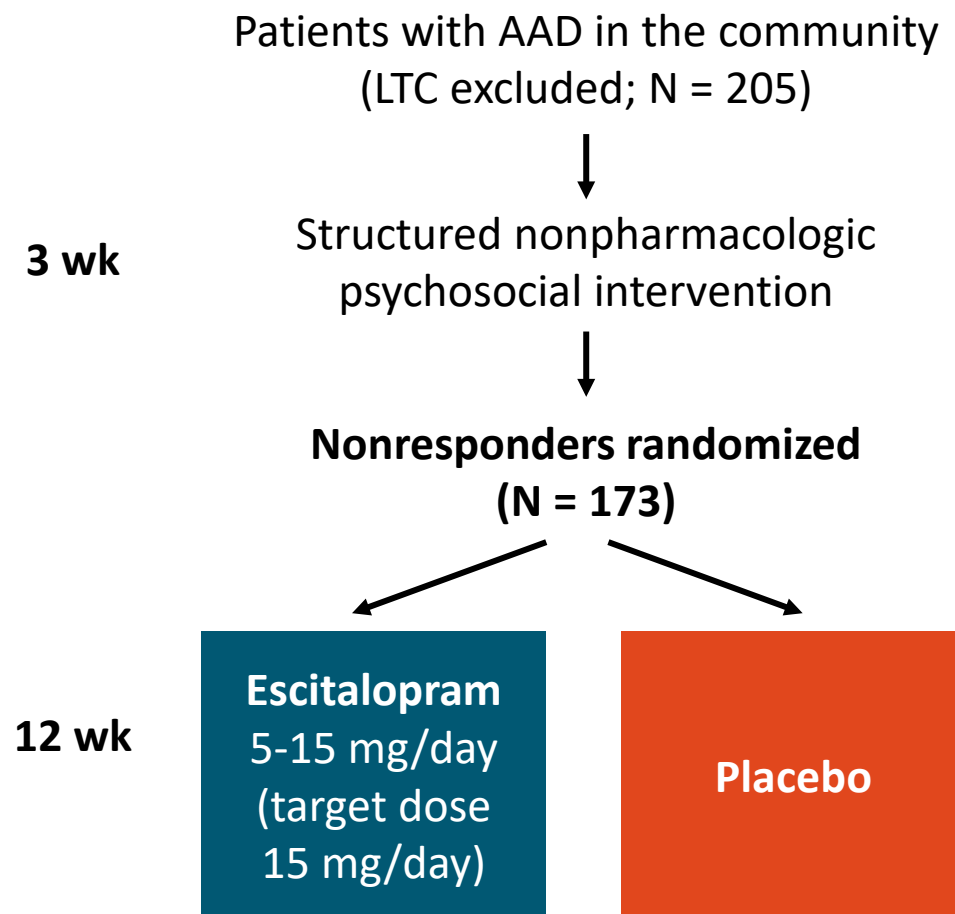
- **Inclusion criteria:**
 - Probable AD, MMSE 5-22
 - IPA criteria for Agitation in Dementia
 - NPI Agitation/Aggression item >4
 - Minimum level of CMAI Aggression
- **Treatments:** 12 wk brexpiprazole 2 or 3 mg QD vs placebo
 - Titration with 3 mg dose after 4 wk
- **Outcomes:** CMAI and CGI
- **Baseline:**
 - Mean MMSE: 15.6; Mean CMAI score: 80
 - 56% moderate dementia; 23% mild; 21% severe
- **Efficacy:** 2 mg or 3 mg dose
 - Greatest benefit in those with high Aggression Factor score
 - Comparison with other atypicals is difficult (likely similar efficacy)
- **Adverse events:**
 - Minimal EPS; some sedation; ? effect on lipids, glucose
 - Possible ↓ cognition, ↑ weight, ↑ mortality?
 - Akathisia in schizophrenia trials



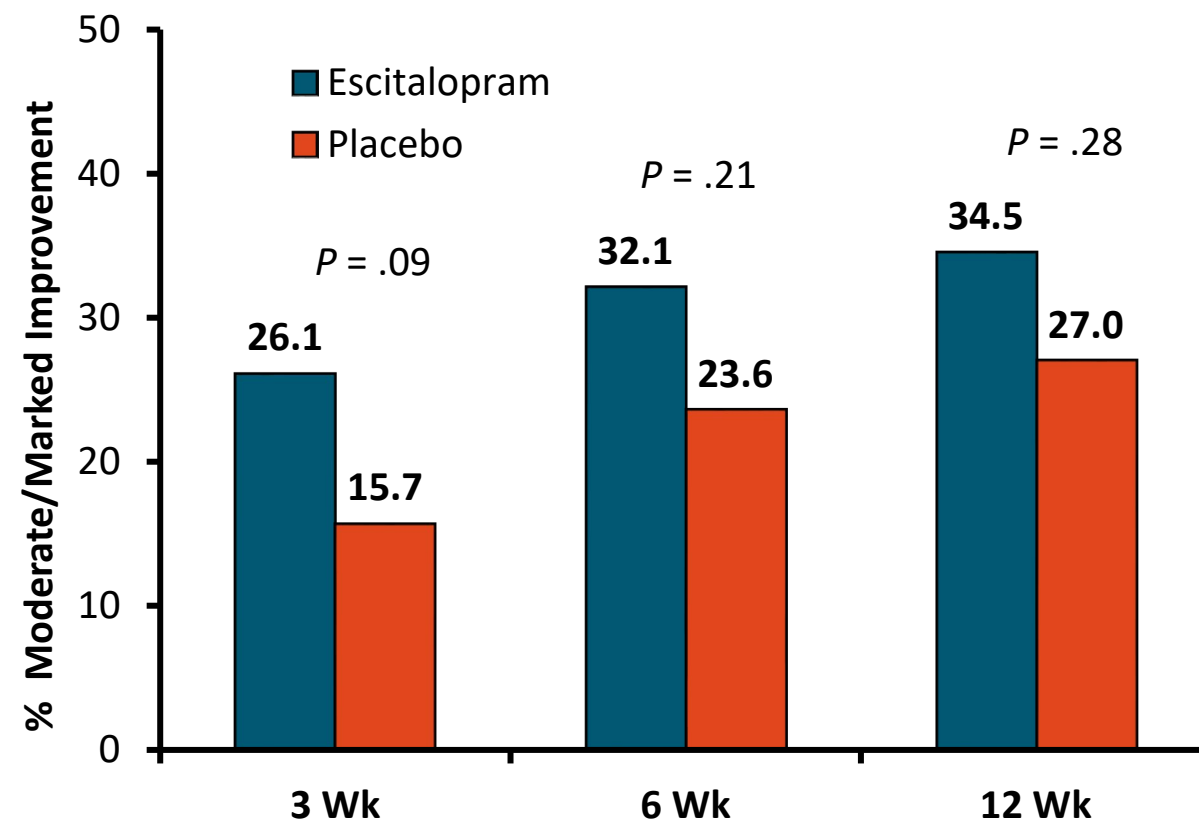
2023 FDA approval for agitation in AD only, not psychosis

- Boxed warning for mortality
- Regular dosing, not PRN
- Initial dose 0.5 mg/d
- Titration to 2 mg or 3 mg/d

S-Citalopram for Agitation in AD (S-CitAD)



Preliminary Results



Ongoing Trials: Agitated/Aggressive Behavior in AD

- **Behavioral Interventions**
 - Including pain management
- **S-citalopram**
- **Pimavanserin, ACP-204**
- **Dextromethorphan/bupropion**
 - AXS-05
- **Cholinergics**
 - Xanomeline (KarXT)
 - Emraclidine
- **5-HT6 antagonists: masuperdine**
- **Oral disintegrating**
 - Dexmedetomidine
 - Lumiteperone
- **THC, cannabidiol**

2024 Alzheimer's Drug Development Pipeline

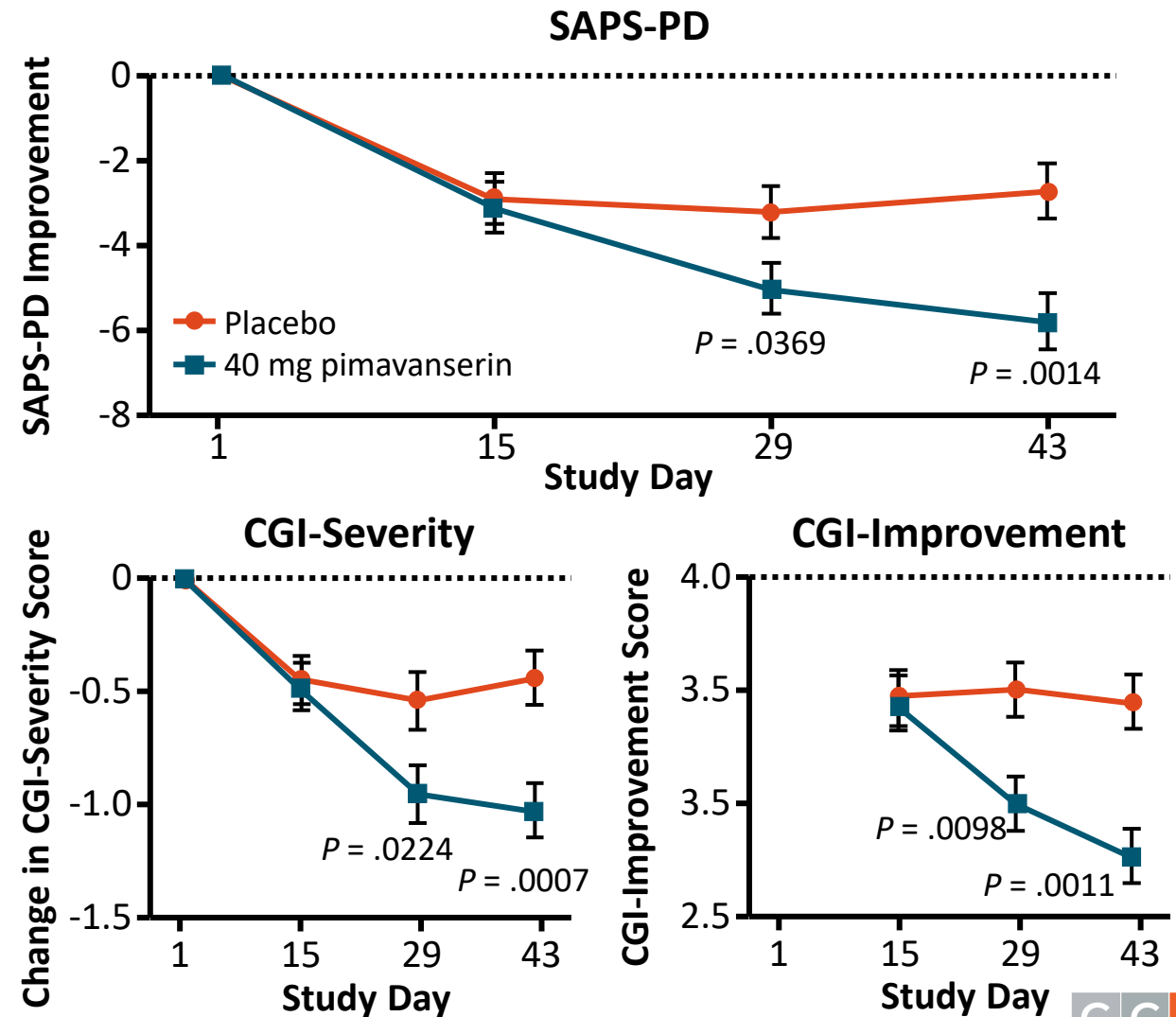


Psychosis: Dementia With Lewy Bodies and Parkinson's Disease

- Lewy body dementia
 - 50%-80% with visual hallucinations
 - Associated with cortical spread and density of Lewy bodies
 - Cholinesterase inhibitor medications may be beneficial
- Parkinson's disease
 - Visual hallucinations common (30%-60%)
 - Dopamine replacement therapy can contribute but is necessary for control of motor symptoms
 - Consider delirium
 - Reassurance
 - If meds are necessary:
 - Quetiapine
 - Pimavanserin
 - Clozapine

Pimavanserin for Parkinson's Disease Psychosis

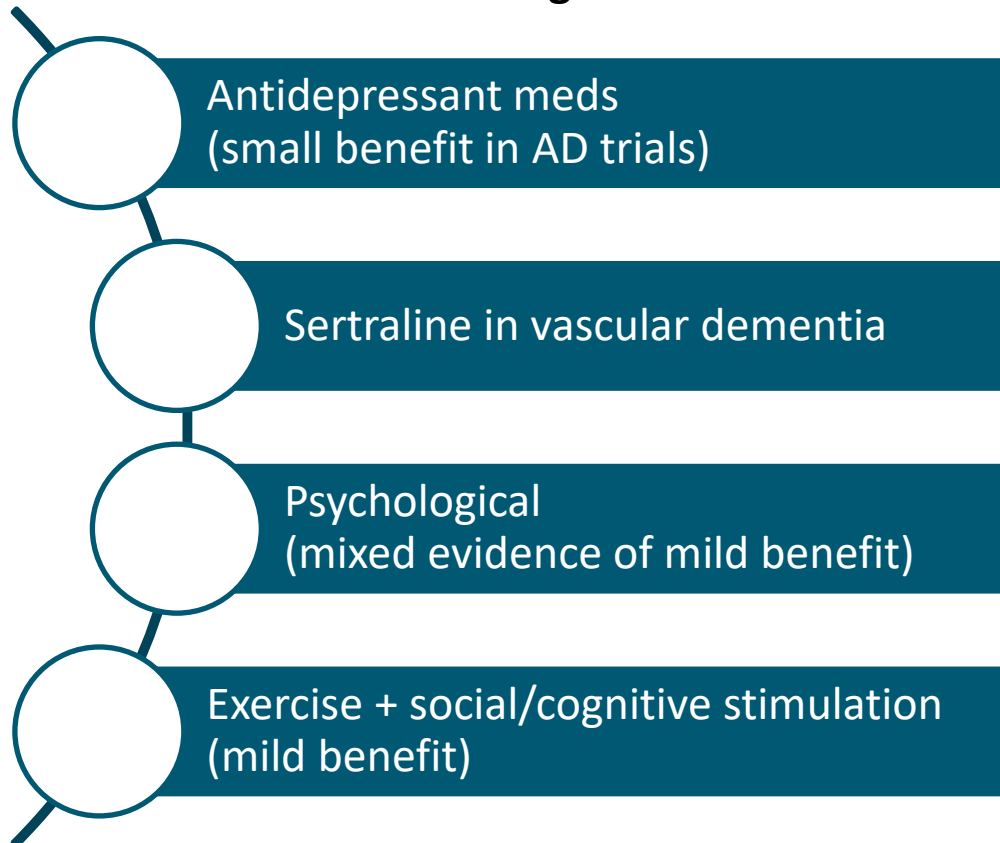
- 5-HT_{2A} inverse agonist
- 6-wk placebo-controlled study
- Primary endpoint: SAPS-PD
 - 9 items, delusions/hallucinations
- CGI responders:
 - 49% pimavanserin vs 26% placebo
- Adverse events
 - Edema 7%
 - Fall 11%
 - Hallucination 7%
 - ↑ QTc
- Usual dose: 34 mg/day



Depression and Anxiety in AD

- Depression is a risk factor for dementia and is particularly common in vascular dementia

Management



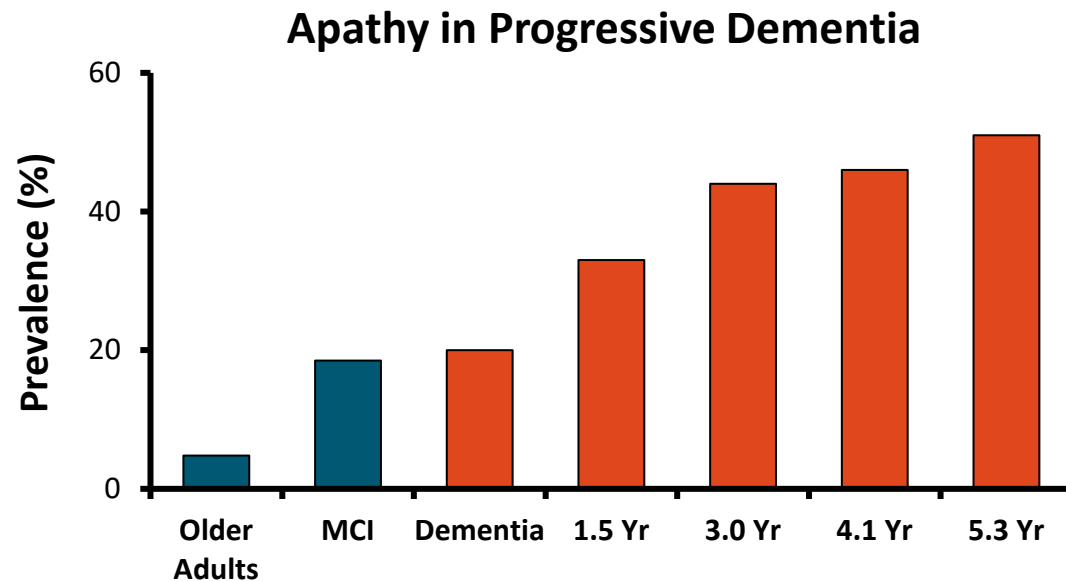
Network meta-analysis saw benefits with:

- + Cognitive stimulation +/- cholinesterase inhibitor
- + Massage/touch therapy
- + Occupational therapy
- + Exercise + social interaction + cognitive stimulation
- + Reminiscence therapy

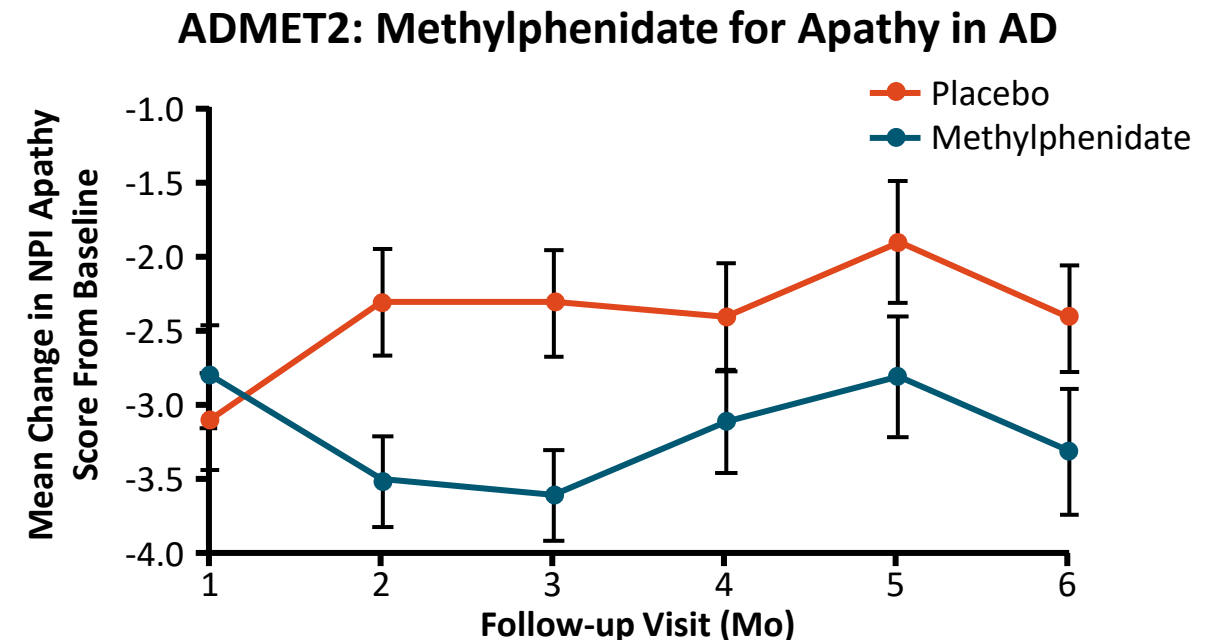
*Some nonpharmacologic interventions
were better than medications*

Apathy in AD

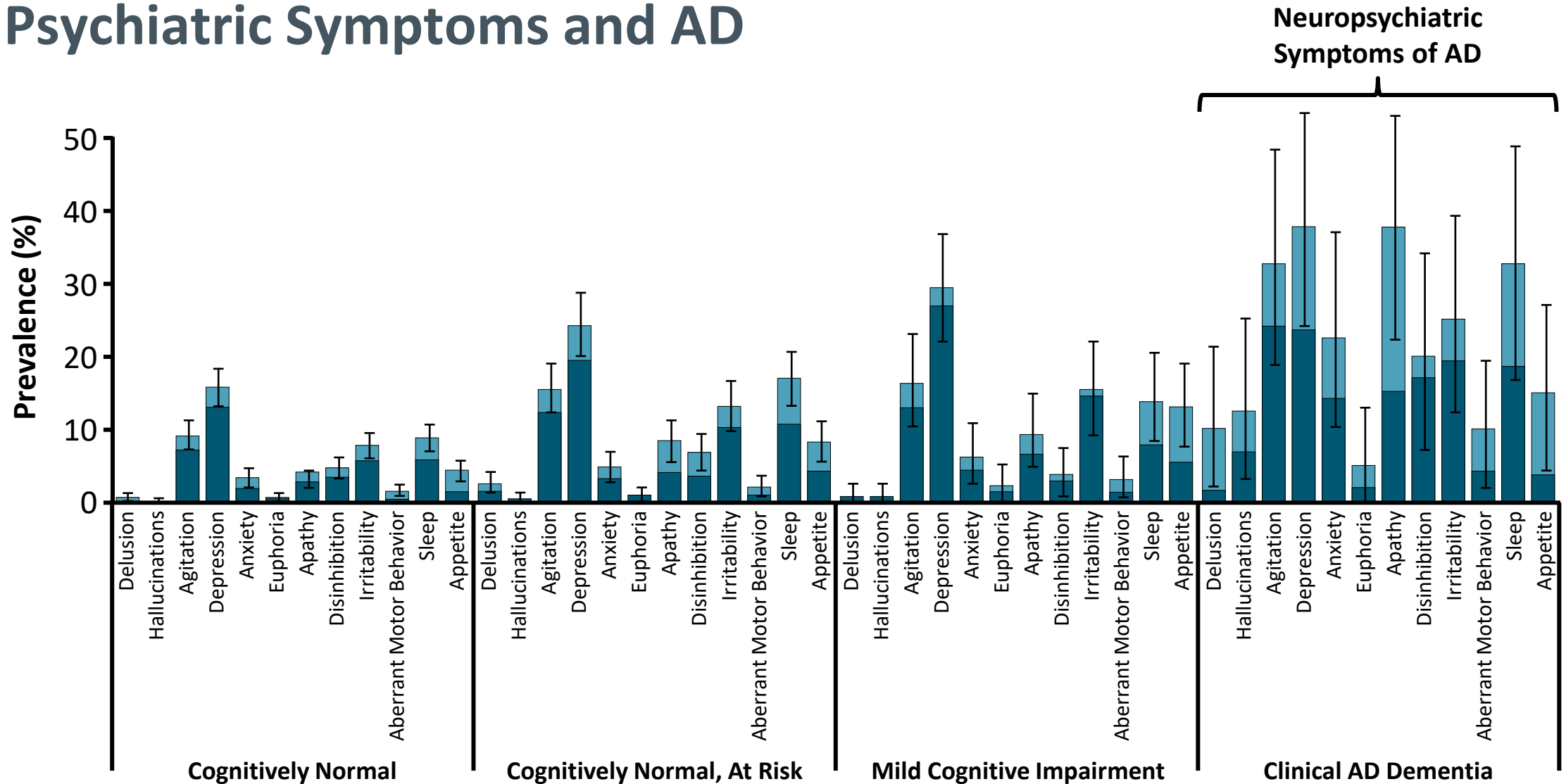
- Apathy in AD is common and persistent
 - Apathy ≠ depression
 - Promotes disability, particularly in MCI
 - Central feature of neurodegeneration



- Neurobiology
 - Brain–behavior relationships
 - Refine nosology
 - Treatment target
- Management
 - Stimulating activities
 - Methylphenidate (up to 10 mg BID)



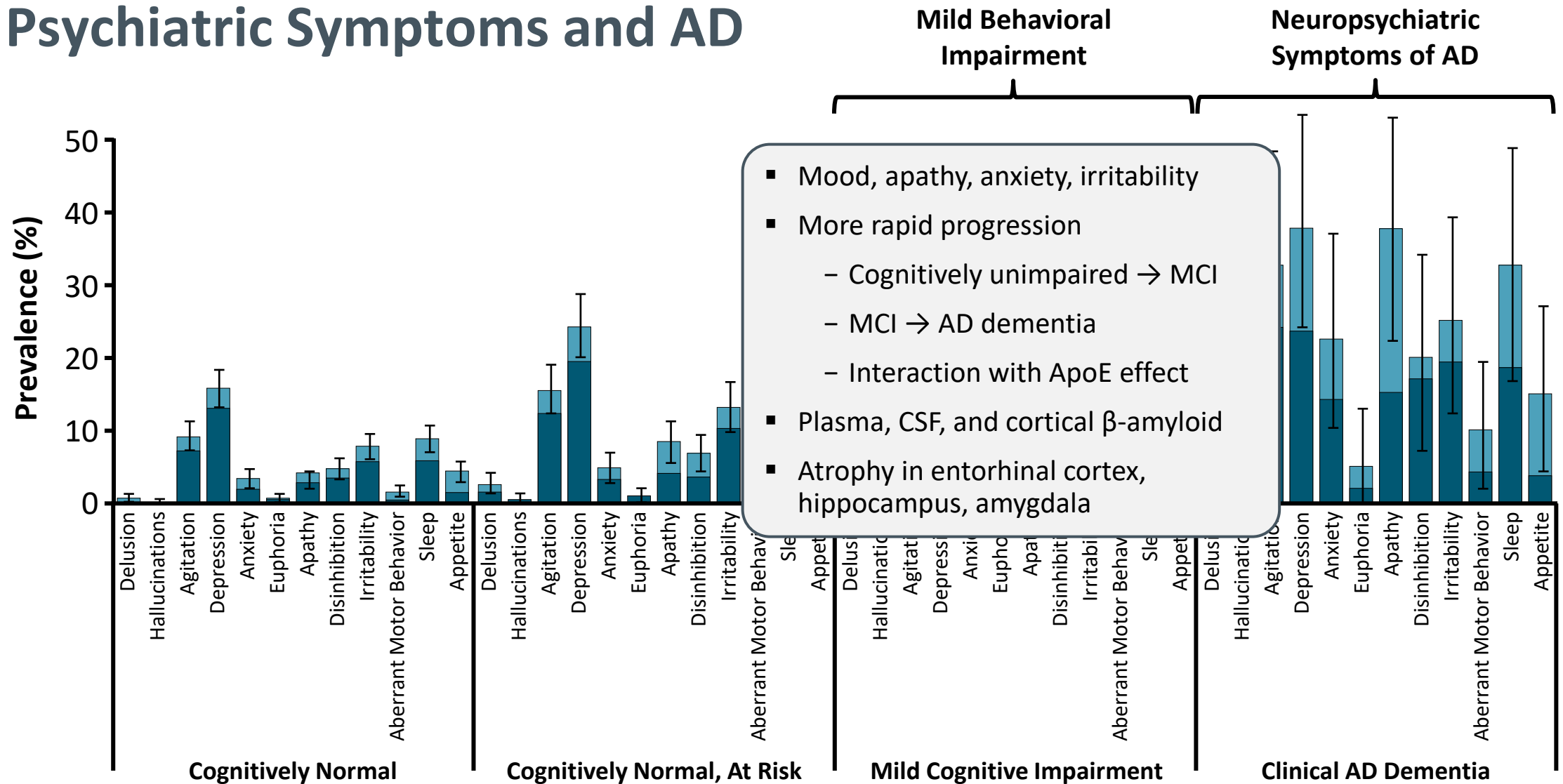
Psychiatric Symptoms and AD



Mortby. J Alzheimers Dis. 2017;59:141. Lewis. J Prev Alzheimers Dis. 2022;9:286. Creese. Alzheimers Res Ther. 2022;14:2. Vellone. Alzheimers Dement (N Y). 2022;19;8:e12370. Krell-Roesch. J Alzheimers Dis. 2020;78:911. Lussier. Alzheimers Dement. 2020 Jan;16:192. Ismail. Alzheimers Dement. 2016;12:195.

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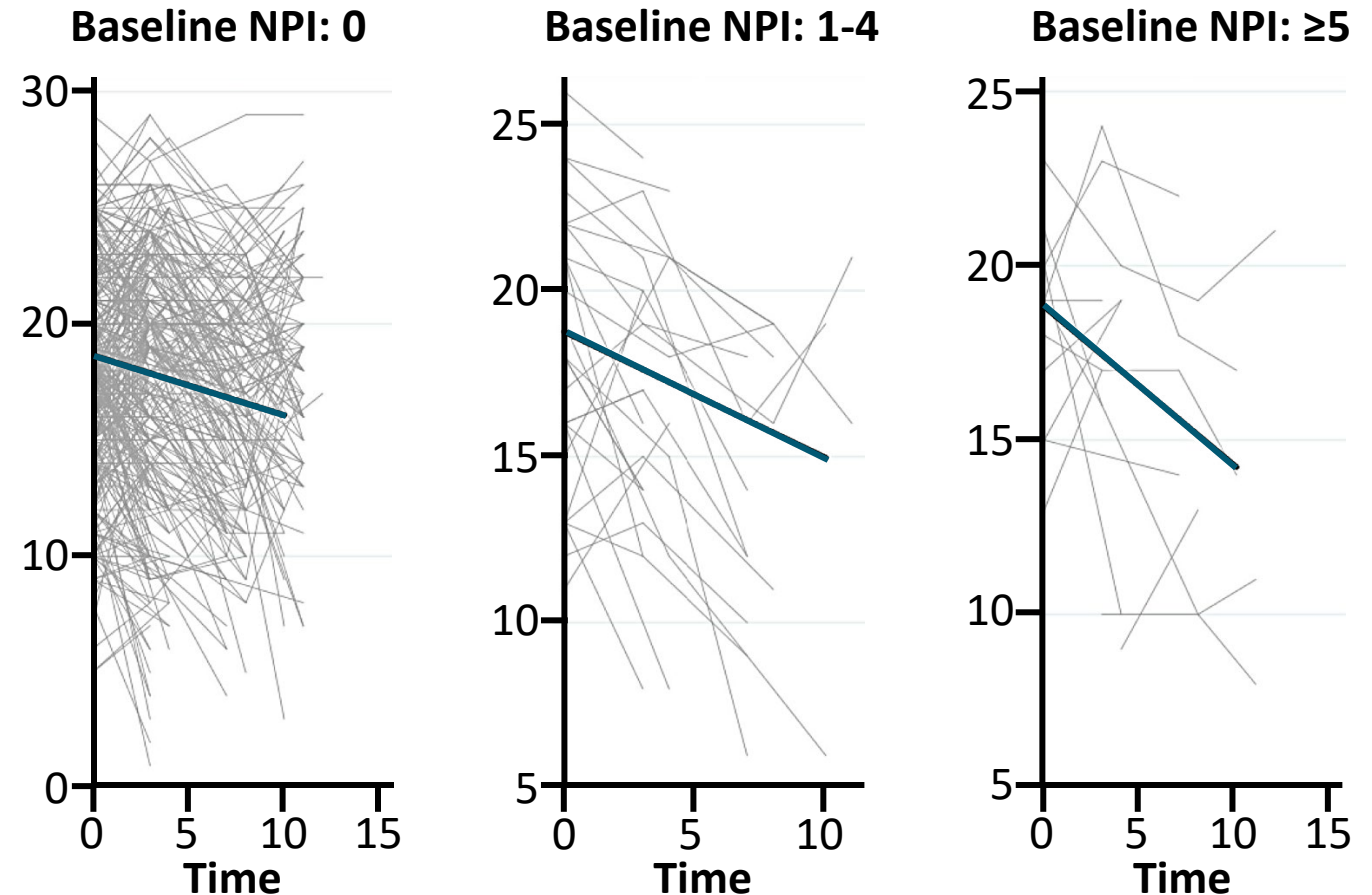
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Neuropsychiatric Symptoms Predict Memory Decline in Healthy Elderly: Cache County Study

- Population-based community sample (N = 470)
 - Cognitively normal
 - Age ≥ 65 yr (Mean: 79)
- NPI at baseline and up to 10 yr follow-up (mean: 5.7 yr)
 - Baseline NPI total score associated with more rapid decline of verbal and visuospatial memory
 - Baseline anxiety associated with more rapid decline of an executive task

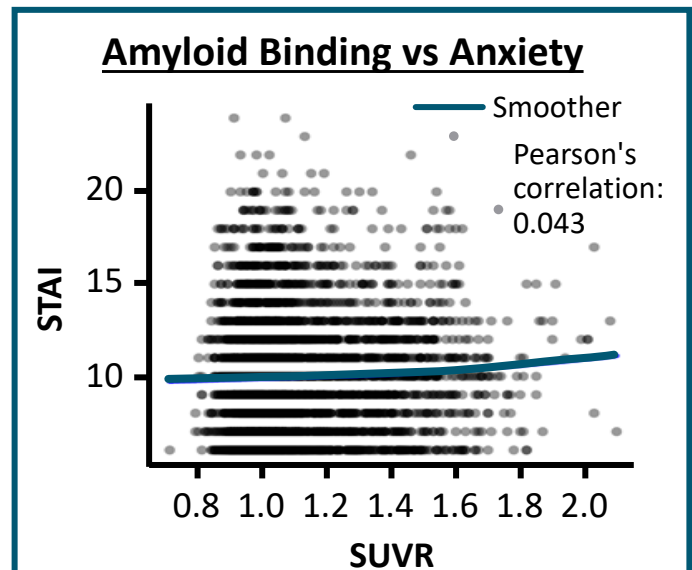
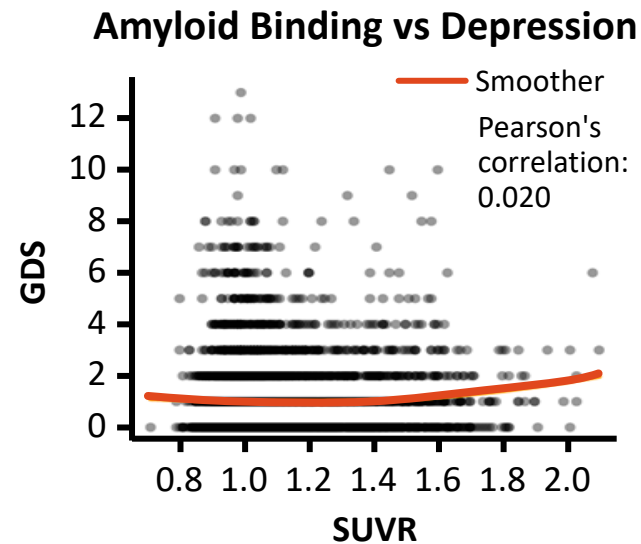
Word List Memory Score Over Time



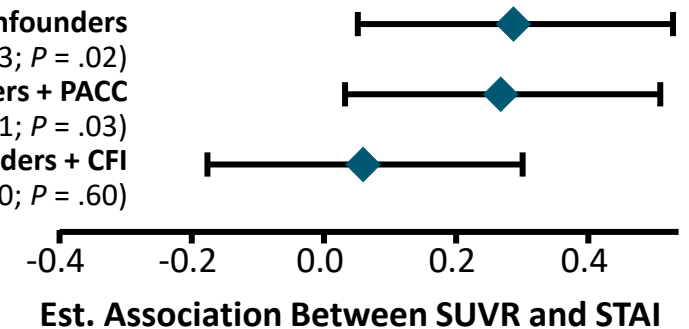
Amyloid Binding, Depression, and Anxiety in Cognitively Unimpaired Older Adults

- **Screening data** from Anti-Amyloid Treatment in Asymptomatic AD (**A4**) study (N = 4342)
 - Mean age: 71
 - Median GDS (depression): 1
 - Median STAI (anxiety): 10
- **PET imaging:** ^{18}F -florbetapir
 - 29% were amyloid positive
 - AD composite area included 6 brain regions

- **Amyloid binding SUVR associated with STAI**
 - Estimated 0.29 points higher per 0.5-point increase in cortical SUVR
 - Self-perceived cognitive difficulties (CFI) attenuated the relationship
 - Objective cognitive deficits (PACC) did not
- **No significant relationship with GDS**



Adjusting for confounders
0.29 (95% CI: 0.05, 0.53; $P = .02$)
Adjusting for confounders + PACC
0.27 (95% CI: 0.03, 0.51; $P = .03$)
Adjusting for confounders + CFI
0.06 (95% CI: -0.17, 0.30; $P = .60$)



Neuropsychiatric Symptoms: 2024 and Beyond

Better-defined syndromes, particularly “agitation”

Biomarkers for distinct symptoms

Medication development guided by neurobiology

Practical, effective, and safe management

- Integrated psychosocial and pharmacologic
- Person-centered and symptom-specific
- Implementation: practice guides and practical strategies
- Healthcare system alliance and improved policies

Integration with new treatments for Alzheimer’s disease and other dementias

Go Online for More CCO Coverage of AD Behavior!

ClinicalThought commentaries with multidisciplinary perspectives

Additional downloadable slidesets from expert faculty with updates on key studies

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