AXSOME THERAPEUTICS

Assessing and Treating Agitation Associated with Alzheimer's Disease

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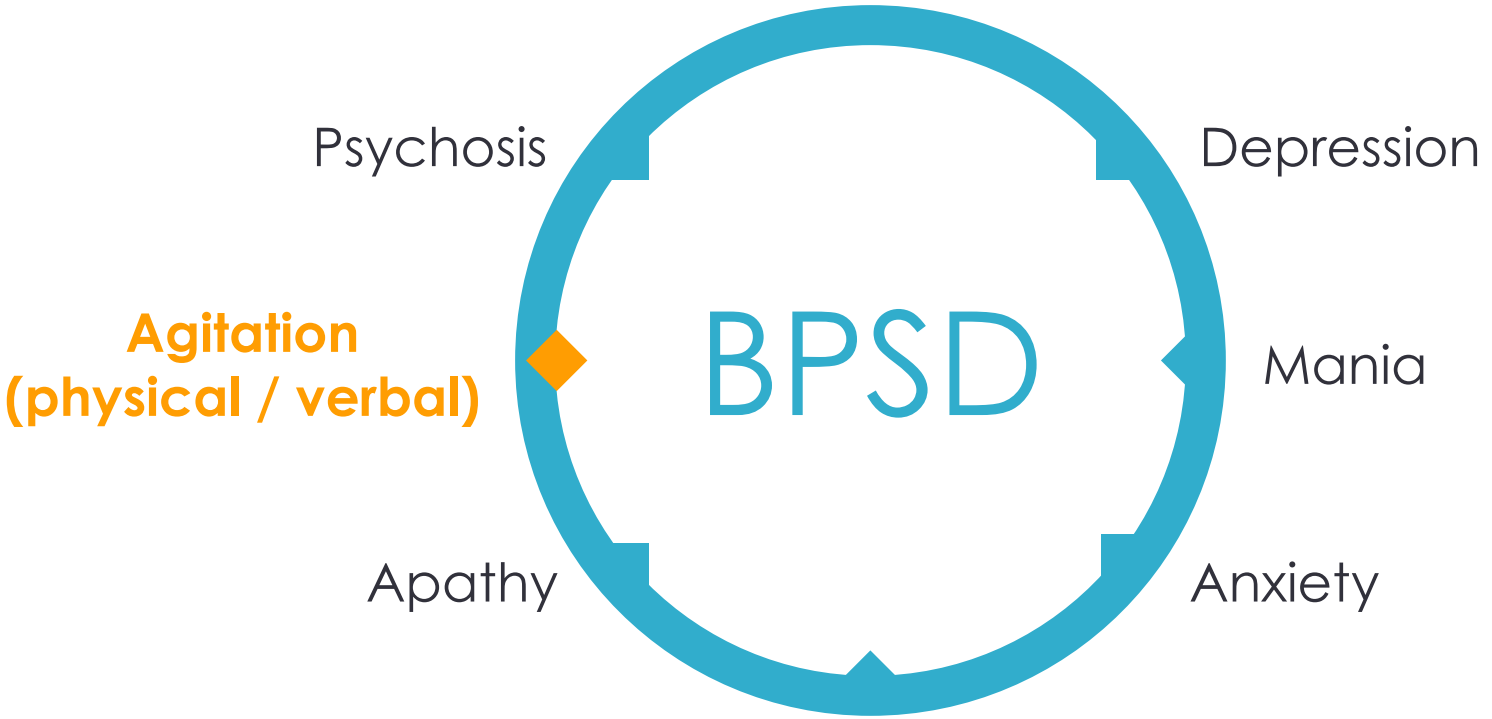
Behavioral and Psychological Symptoms of Dementia (BPSD)



Wandering | Excessive motor activity | Intrusiveness
Resistance | Disinhibition | Sleep disturbances

Lyketsos CG, Carrillo MC, Ryan JM, et al., *Alzheimers Dement* 2011;7:532-539.

Agitation

According to the International Psychogeriatric Association (IPA), agitation involves **excessive motor activity**, or **verbal** or **physical aggression** that causes observed (or inferred) emotional distress, and is “severe enough to produce excess disability” along with significant impairment in interpersonal relationships, social functioning, and/or the ability to perform or participate in daily living activities.

Cummings J, Mintzer J, Brodaty H, et al., *Int Psychoger* 2015;27(1):7-17.

Agitation According to Cohen-Mansfield

- Jiska Cohen-Mansfield stresses that agitation is NOT a diagnosis but a group of behaviors.
- She and her colleague defined agitation as **inappropriate verbal, vocal, or motor activity** that is not judged by an outside observer to result directly from the perceptible needs or confusion of the agitated individual.[1]
- She developed the **Cohen-Mansfield Agitation Inventory (CMAI)** as a scale to assess the frequency of a variety of agitated behaviors within the preceding two weeks in an individual.
- There are three categories of agitated behaviors in the CMAI: verbally agitated, non-aggressive agitated behaviors, and aggressive behaviors.

[1]Cohen-Mansfield J, Bilig N, *J Am Geriatr Soc* 1986;34(10):711-721.

Agitation on the CMAI

- Repeated sentences or questions
- Verbal interruptions
- Making strange noises
- Screaming
- Complaining
- Unwarranted requests for agitation
- Negativity / uncooperativeness
- Cursing / verbal aggression
- Spitting
- Verbally bossy or pushy
- Sexual advances
- Restlessness
- Pacing / wandering
- Trying to get out / sneak out
- Dressing / undressing inappropriately
- Hiding / hoarding
- Temper outbursts
- Hitting / kicking
- Throwing things /destroying property
- Grabbing / clinging / pushing
- Biting / scratching
- Hurting self / others
- Falling intentionally
- Eating / drinking nonfood substances

The Burden of Agitation

80-90% patients with dementia demonstrate various forms of BPSD

Agitation is associated with accelerated disease progression with disproportionate reductions in daily function and well-being, increased healthcare utilization and costs, increased risk of injury to self and others, higher rates of institutionalization, increased mortality, and significantly worse caregiver stress and overall burden.

Selbæk et al., *Int Psychoger* 2014;26:81-9.
Murman et al.,*Neurol* 2002;59:1721–1729.
Herrmann et al., *Can J Psychiatry* 2015;60:189-99.
Okura et al., *JAGS* 2011;59:473–48.
Van Den Wijngaart et al., *Aging Ment Health* 2007;11:626-36.

The Cost of Agitation

- Alzheimer's disease affects an estimated 5.3 million individuals in the United States and 50 million people worldwide, a number that is expected to double in 20 years.
- As of 2015, the aggregated cost of care for all individuals with Alzheimer's disease and other dementias is estimated at $226 billion, eclipsing the costs of both heart disease and cancer, with 63% of this cost covered by Medicare and Medicaid.
- One study estimated that a 1-point worsening of the neuropsychiatric inventory score is associated with an incremental increase of between $247 - $409 per year in total direct costs of care. This cost data is over 10 years old and is likely much higher now.

Alzheimer's Association, 2015;11(3):332-84.
Hurd et al., *N Eng J Med* 2013;368(14):1326-34.
Murman & Colenda, *Pharmacoeconomics*, 2005;23(3):227-42.

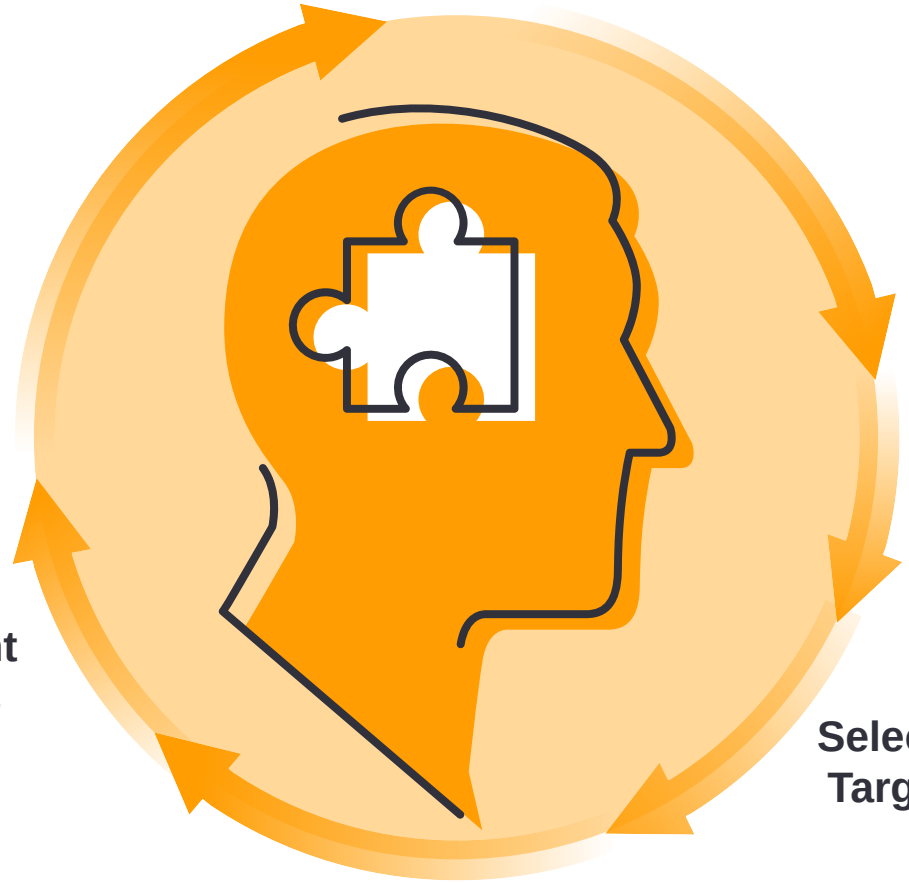
Clinical Assessment

- Caregivers may bear the burden of agitation and not tell their doctors
- Agitation is often not demonstrated in routine doctor visits
- Agitation may cause caregivers to stop taking the person out, restrict visits with others, avoid doctor visits, or seek premature institutionalization
- Agitation can cause injury to patients and caregivers
- Clinicians need to actively ask about the variety of symptoms

How to Evaluate and Treat Agitation

Identify, Document, Analyze Behaviors [Review ABC's]

Re-evaluate if no response:
- Correct target symptoms?
- Untreated causes?
- Revise, retry behavioral approach
- Try alternate medication or augmentation



Identify Potential Causes:
- Medical
- Psychiatric
- Environmental
- Behavioral

Address Readily Reversible Causes

Select Appropriate Target Symptoms

Implement Behavioral Approaches, including Therapeutic Programs

Consider Low-dose Pharmacologic Agent to Match Symptoms

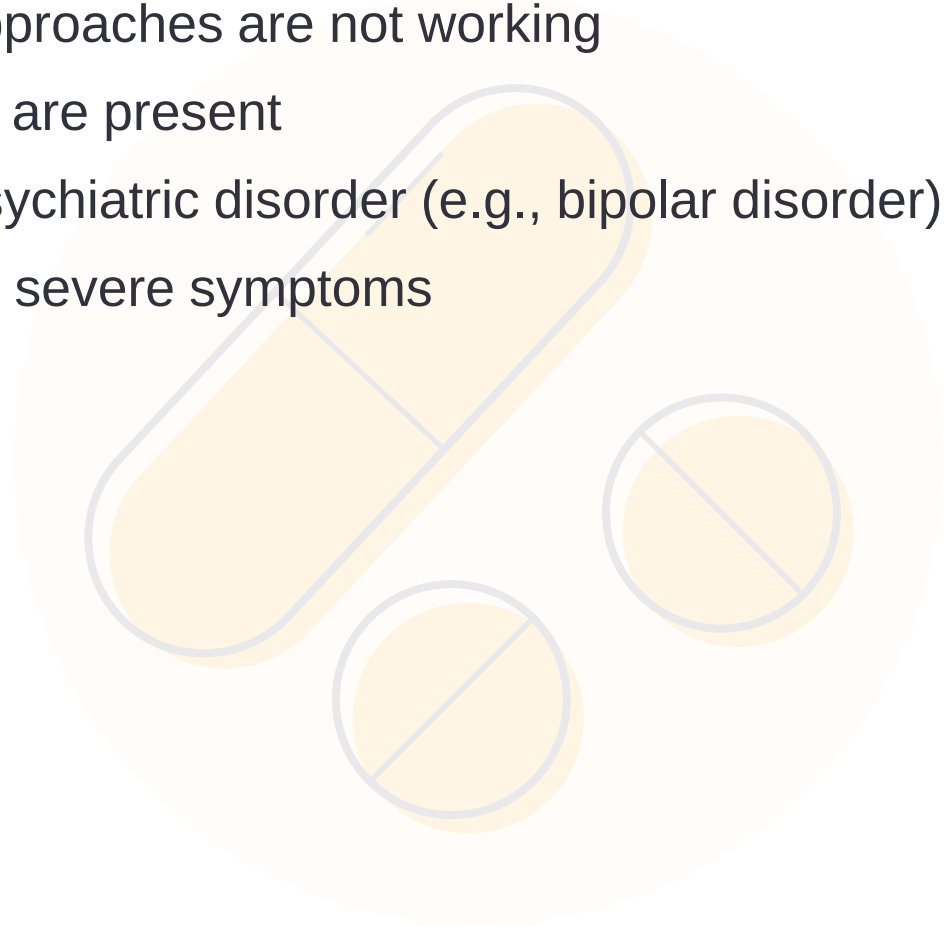
The DICE Algorithm

DOMAIN	ELEMENTS
Describe	Obtain description of behaviors from caregivers; Review the context of the behaviors (e.g., when, where, with whom)
Investigate	Examine patient factors (e.g., medical and psychiatric conditions, and medications), caregiver factors, environmental factors, and cultural factors
Create	Team approach to respond to physical problems, develop behavioral approaches, and devise pharmacologic approach
Evaluate	Evaluate the degree of implementation of the plan and the overall results

Kales HC, Gitlin LN, Lyketsos CG, et al., *J Am Ger Soc* 2014;62(4):762-9.

When are Medications Needed?

- Behavioral approaches are not working
- Other BPSDs are present
- Underlying psychiatric disorder (e.g., bipolar disorder)
- Dangerous or severe symptoms



Treatment Dilemmas

- There is no FDA-approved medication for the treatment of agitation associated with Alzheimer's disease, or general BPSD.
- All psychotropic medication use is thus considered "off-label".
- Many studies use small samples, multiple instruments, variable definitions, limited samples, are not always controlled and have high placebo responses.
- Clinical trials of agitation in dementia have not established significant efficacy for any psychotropic medications.

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

Alterations in Neurotransmitter Systems: Relevance to AD Agitation and other BPSDs

Altered Glutamate Transmission via NMDA

- Pooled analysis suggests memantine (NMDA receptor antagonist) decreased the emergence of agitation, reduced agitation severity, and stabilized agitation symptoms compared to ChEIs alone.[1]

Reduced Sigma-1

- Positron emission tomography (PET) demonstrated a lower density of sigma-1 receptors in AD patients as compared to age-matched controls.[2]

Deficiency in Serotonin

- Citalopram (SSRI) decreased agitation compared to placebo in AD patients. Results tempered by negative cognitive and cardiovascular effects.[3]

Dopamine Deficits

- Bupropion (dopamine reuptake inhibitor) results in improvements in other BPSDs seen in AD patients (apathy, depression).[4]
- Dopaminergic deficits may render individuals more sensitive to developing spontaneous and drug-induced movement disorders.

[1]Atri A, Agronin M, et al., *Neurology* 2018;90(15):P6.175.
[2]Mishina et al., *Ann Nucl Med* 2008;2(22):151-6.
[3]Porsteinsson AP et al., *Hum Psychopharmacol* 2010;25(3)193-200.
[4]Corcoran C, Wong ML, O'Keane V, *J Psychopharmacol* 2004;1(18):133-5; Marin RS et al., *J Neuropsychiatry Clin Neurosci* 1995;7(1):23-30; Steinberg H et al., *Int J Geriatr Psychiatry* 2008;2(23):170-7.

AXS-05 Pharmacology:
Relevance to AD Agitation and other BPSDs

Mechanism of Action	DM	BUP	AXS-05 DM+BUP
NMDA Receptor Antagonist	✓		✓
Sigma-1R Agonist	✓		✓
Norepinephrine Reuptake Inhibitor	✓	✓	✓
Serotonin Reuptake Inhibitor	✓		✓
Dopamine Reuptake Inhibitor		✓	✓
Nicotinic ACh Receptor Antagonist	✓	✓	✓

DM = Dextromethorphan; BUP = Bupropion. ✓ Present

AXS-05

- Fixed-dose combination of Dextromethorphan (DM) and Bupropion.
- Bupropion inhibits DM metabolism, and increases DM concentrations.

Clinical Evidence Suggests

- DM and Bupropion target neurotransmitter systems that are altered and that disrupt behavior in AD.

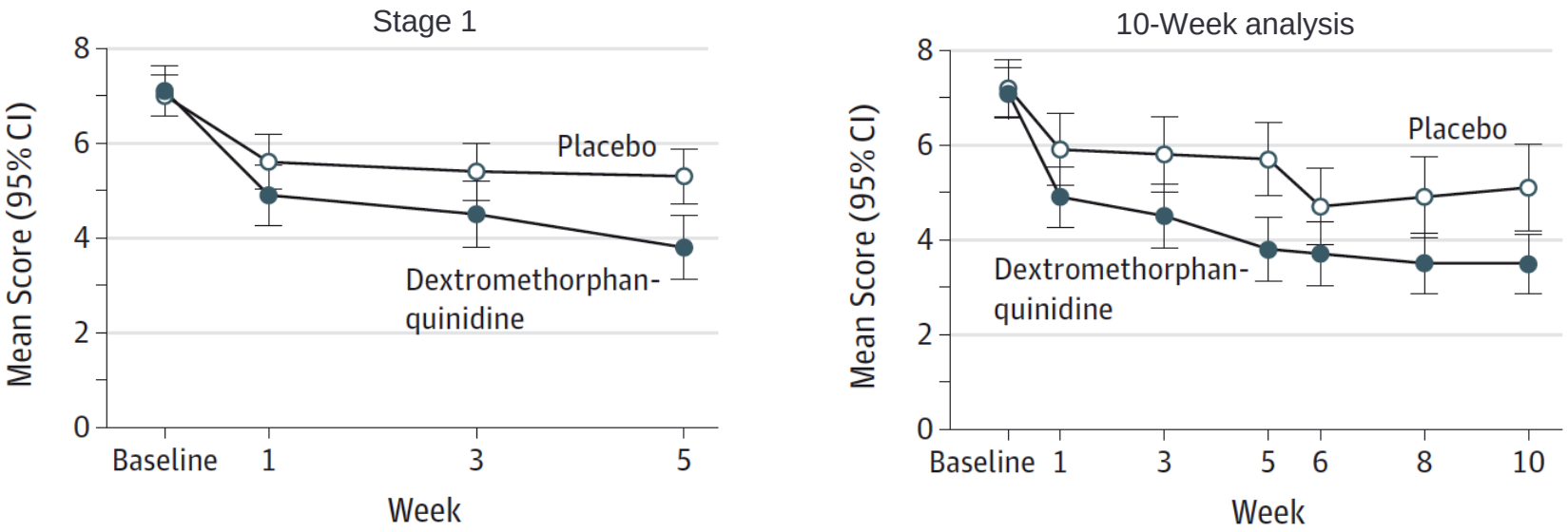
DM + Quinidine Effect on Agitation in Patients Alzheimer's Disease Trial

- Quinidine, like bupropion, is a metabolic inhibitor that increases DM concentrations.
- Randomized, double-blind, placebo-controlled, two-stage trial:
  - Placebo (n=125), 30 mg DM + 10 mg quinidine (Q) (n=93), for stage 1
- Two consecutive 5-week stages
- Inclusion criteria:
  - Patients with probable Alzheimer's disease
  - Clinically significant agitation (Clinical Global Impressions–Severity agitation score 4 or above)
  - Mini-Mental State Examination score of 8 to 28
- Stable dosages of antidepressants, antipsychotics, hypnotics, and antidementia medications were allowed.
- Primary endpoint: change on the Neuropsychiatric Inventory (NPI) Agitation/Aggression domain – scale range, 0 (absence of symptoms) to 12 (symptoms occur daily and with marked severity).

Cummings JL et al., *JAMA* 2015;12(314):1242-54.

Dextromethorphan with Metabolic Inhibition Reduces Agitation in AD

Mean Neuropsychiatric Inventory Agitation/Aggression Domain Scores



- DM+Q treatment reduced NPI Agitation/Aggression scores by 46% vs. 24% for placebo (P<0.001) at 5 weeks.
- Results also significant for stage 2 and, at 10 weeks (P=0.002)
- Adverse events included falls (8.6% for dextromethorphan-quinidine vs 3.9% for placebo), diarrhea (5.9% vs 3.1% respectively), and urinary tract infection (5.3% vs 3.9% respectively).
- Dextromethorphan-quinidine was not associated with cognitive impairment or sedation.

Cummings JL et al., *JAMA* 2015;12(314):1242-54.

Dextromethorphan with Metabolic Inhibition
Improvements in Secondary Measures

Table 2. Summary of Efficacy Outcome Measures in the Modified Intention-to-Treat Population

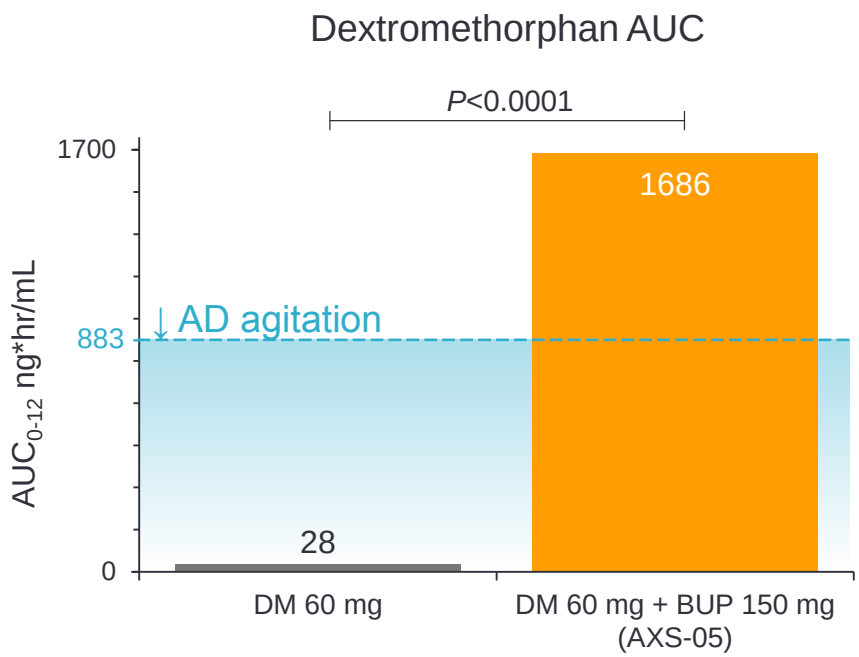
Outcome Measure and Study Stage[a]	No. of Participants		Change From Baseline, Mean (95% CI)		*P* Value by Stage[b]	Least Squares Mean Treatment Difference (95% CI)[c]	*P* Value by SPCD[b,d]
	Dextromethorphan-Quinidine	Placebo	Dextromethorphan-Quinidine	Placebo			
NPI Agitation/Aggression domain[e]							
Stage 1[a]	93	125	−3.3 (−3.9 to −2.6)	−1.7 (−2.3 to −1.2)	<.001	−1.5 (−2.3 to −0.7)	<.001
Stage 2[a]	44	45	−2.0 (−3.0 to −1.0)	−0.8 (−1.9 to 0.2)	.02	−1.6 (−2.9 to −0.3)	
10 wk[f]	93	66	−3.6 (−4.3 to −2.9)	−1.9 (−2.8 to −1.0)	.001	−1.8 (−2.8 to −0.7)	.003
NPI4A composite[e]							
Stage 1[a]	93	125	−7.3 (−9.1 to −5.4)	−4.5 (−6.0 to −3.0)	.03	−2.4 (−4.6 to −0.2)	.001
Stage 2[a]	44	45	−4.8 (−6.9 to −2.7)	−1.4 (−3.8 to 1.0)	.01	−3.9 (−7.0 to −0.9)	
10 wk[f]	93	66	−8.5 (−10.4 to −6.7)	−5.0 (−7.4 to −2.5)	.01	−3.4 (−6.1 to −0.7)	NA
NPI4D composite[e]							
Stage 1[a]	93	125	−7.6 (−9.4 to −5.7)	−4.0 (−5.5 to −2.6)	.006	−3.0 (−5.1 to −0.9)	<.001
Stage 2[a]	44	45	−4.6 (−6.8 to −2.4)	−1.9 (−4.2 to 0.4)	.02	−3.5 (−6.5 to −0.5)	
10 wk[f]	93	66	−8.3 (−10.1 to −6.5)	−5.0 (−7.4 to −2.6)	.02	−3.0 (−5.5 to −0.4)	NA
NPI Caregiver Distress agitation score[e]							
Stage 1[a]	93	125	−1.4 (−1.6 to −1.0)	−0.6 (−0.8 to −0.4)	<.001	−0.7 (−1.0 to −0.3)	.01
Stage 2[a]	44	45	−0.5 (−0.9 to −0.004)	−0.7 (−1.2 to −0.2)	.49	−0.2 (−0.8 to 0.4)	
10 wk[f]	93	66	NA	NA	NA	NA	NA
Cornell Scale for Depression in Dementia[g]							
Stage 1[a]	88	123	−1.0 (−1.8 to −0.3)	0.6 (−0.1 to 1.3)	.002	−1.6 (−2.5 to −0.6)	.02
Stage 2[a]	43	44	−0.9 (−1.8 to −0.004)	−0.7 (−1.5 to 0.1)	.75	−0.2 (−1.3 to 0.9)	
10 wk[f]	88	64	−1.2 (−2.0 to −0.4)	0.4 (−0.6 to 1.5)	.03	−1.3 (−2.6 to −0.1)	NA

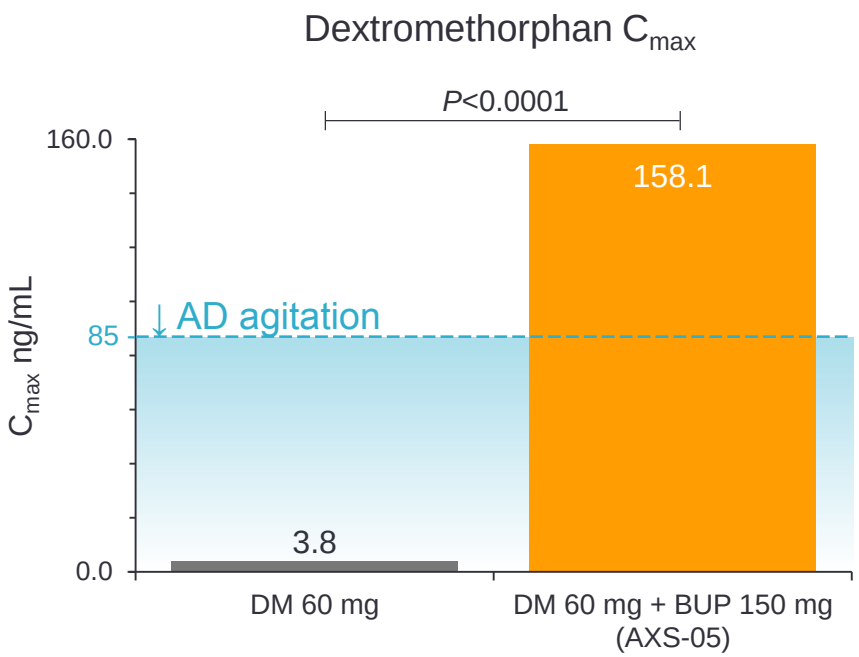
Symptom cluster which approximates the scope of behaviors assessed by the CMAI

Cummings JL et al., *JAMA* 2015;12(314):1242-54.

AXS-05 Results in DM Concentrations Relevant for AD Agitation

DM Concentrations with AXS-05 and Therapeutic DM Levels for AD Agitation





- AXS-05 data from Phase 1 pharmacokinetic trial.
- Dotted line shows DM plasma concentrations reported with dose (DM 30 mg + Q 10 mg) resulting in reduction of agitation symptoms in AD patients.

Axsome data on file.
Therapeutic DM concentrations from NDA 021879, FDA Clinical Pharmacology Review.
DM, Dextromethorphan; Q, Quinidine; BUP, Bupropion; AD, Alzheimer's disease; PBA, pseudobulbar affect

Bupropion May Target other BPSDs in AD

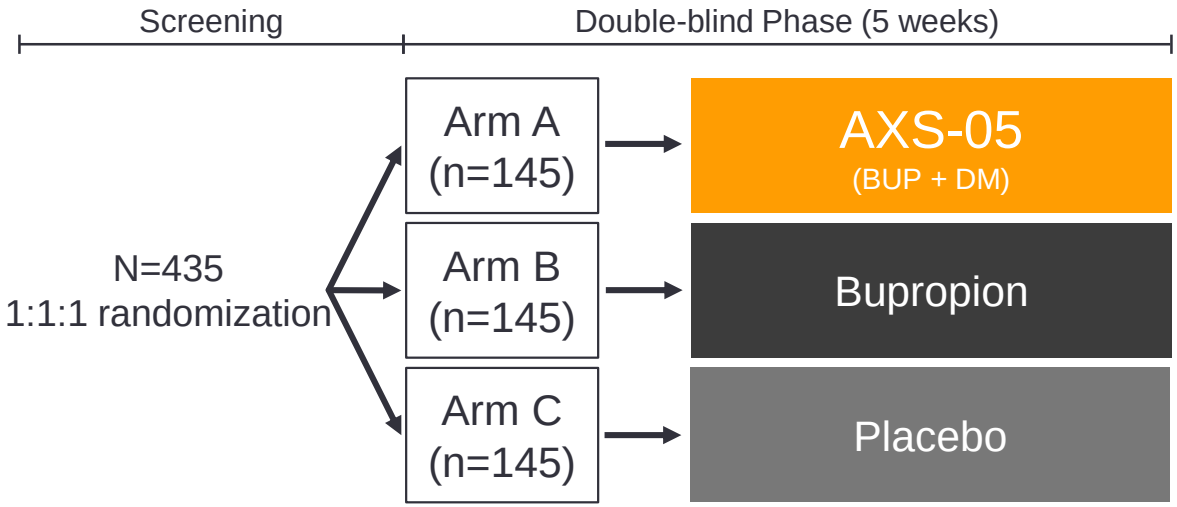
- Depression is the most common neuropsychiatric symptom in patients with AD with a reported 5-year period prevalence of 77%[1]
  - Bupropion is a well-established antidepressant.
- Apathy is another common neuropsychiatric symptom in patients with AD, with a reported 5-year period prevalence of 71%[1]
  - Case studies have indicated that bupropion may be efficacious in treating apathy.[2]
- Anxiety is a neuropsychiatric symptom reported in 62% of patients with AD over a 5-year period[1]
  - Several clinical studies suggest that bupropion is able to reduce anxiety[3]

[1]Steinberg H et al., *Int J Geriatr Psychiatry* 2008;2(23):170-7.
[2]Corcoran C, Wong ML, O'Keane V, *J Psychopharmacol* 2004;1(18):133-5; Marin RS et al., *J Neuropsychiatry Clin Neurosci* 1995;7(1):23-30.
[3]Bystritsky A et al., *Psychopharmacol Bull* 2008;1(41):46-51; Rush AJ et al., *Am J Psychiatry* 2006;11(163):1905-17.

AXS-05 Is Being Evaluated in a Phase 2/3 Trial in AD Agitation

ADVANCE STUDY

A Phase 2/3 trial to assess the efficacy and safety of AXS-05 in the treatment of Agitation in AD.



BUP = Bupropion; DM = Dextromethorphan.

- **Primary Endpoint:** Cohen-Mansfield Agitation Inventory (CMAI).
- **Key Inclusion Criteria:**
  - Diagnosis of probable Alzheimer's disease
  - Clinically significant agitation
- Interim Analysis for Futility: At approximately 30% target subjects.
- Interim Analysis for Efficacy: At approximately 60% target subjects.

Summary

- Alzheimer's disease is extremely prevalent and will double in the next 20 years.
- Agitation is one of the most common psychiatric symptoms associated with AD, and causes significant worsening of AD symptoms, patient suffering, safety concerns, caregiver burden and overall cost of treatment.
- There are no FDA-approved agents for the treatment of agitation in AD.
- Agitation is believed related to both structural and functional damage to the brain, including effects on glutamatergic, serotonergic and dopaminergic pathways.
- The pharmacology of AXS-05 targets neurotransmitter systems believed to be altered in AD agitation.
- The DM component of AXS-05 has been shown reduce agitation when dosed with quinidine in a placebo-controlled trial.
- DM concentrations achieved with AXS-05 are in the therapeutic range for DM efficacy in agitation measured using the NPI.
- A Phase 2/3 trial of AXS-05 in AD patients with agitation is ongoing.

Q&A

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Thank you.

For more information, please contact

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