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Neuropsychiatry of Alzheimer's disease

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<http://nearesearch.bwh.harvard.edu>

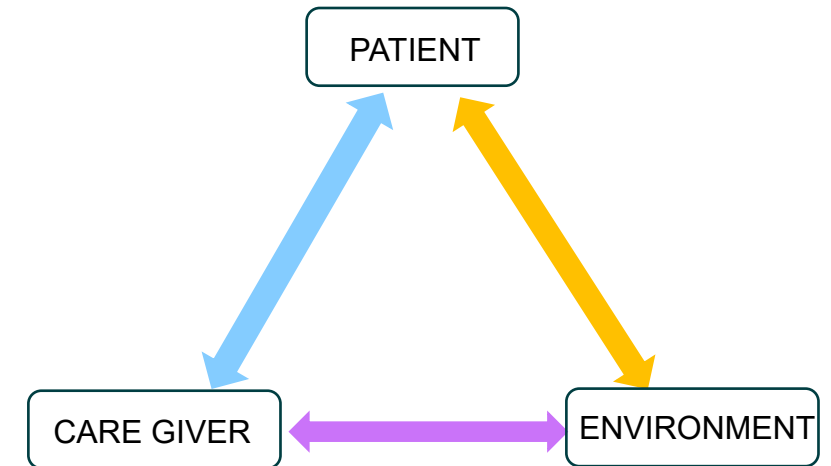
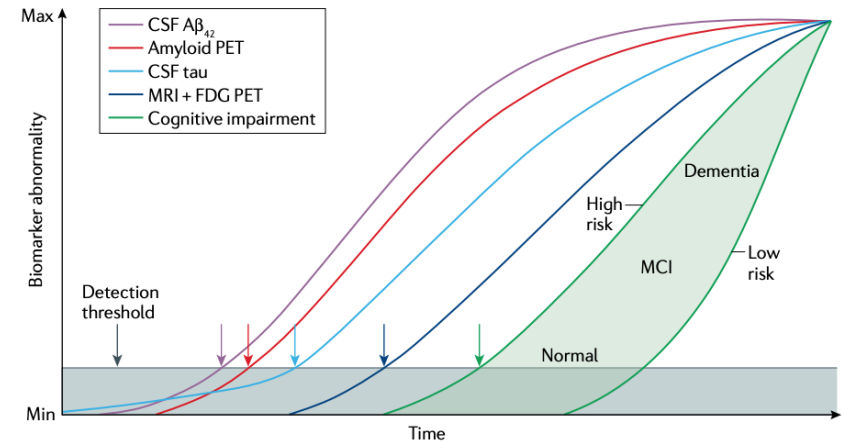
Disclosures

Neither I nor my spouse has a relevant financial relationship with a commercial interest to disclose.

I will be discussing the off-label use of psychotropic medications for the treatment of neuropsychiatric symptoms of dementia.

Overview

- Alzheimer's disease as biologic process encompassing preclinical, mild cognitive impairment and dementia states
- Neuropsychiatric symptoms (NPS) include disorders of perception, thought, behavior and affect
- Theoretical models of NPS
- Diagnostic workup of NPS
- Recommended approached and evidence-based treatment of NPS



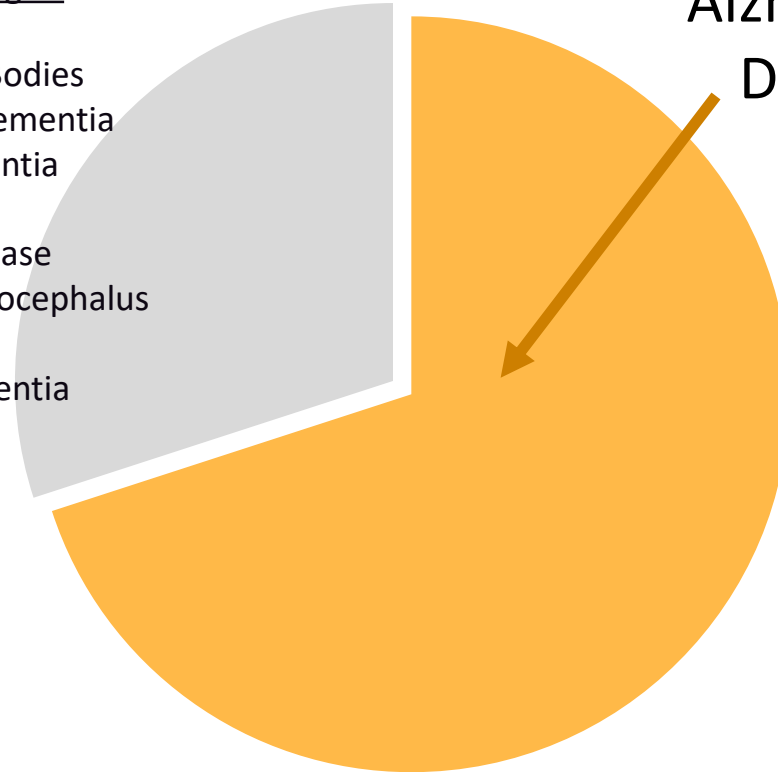
Alzheimer's disease (AD)

AD is the most common neurodegenerative disorder and cause of dementia (60-80% of cases - 1° AD or mixed dementia).

Other Dementia Etiologies

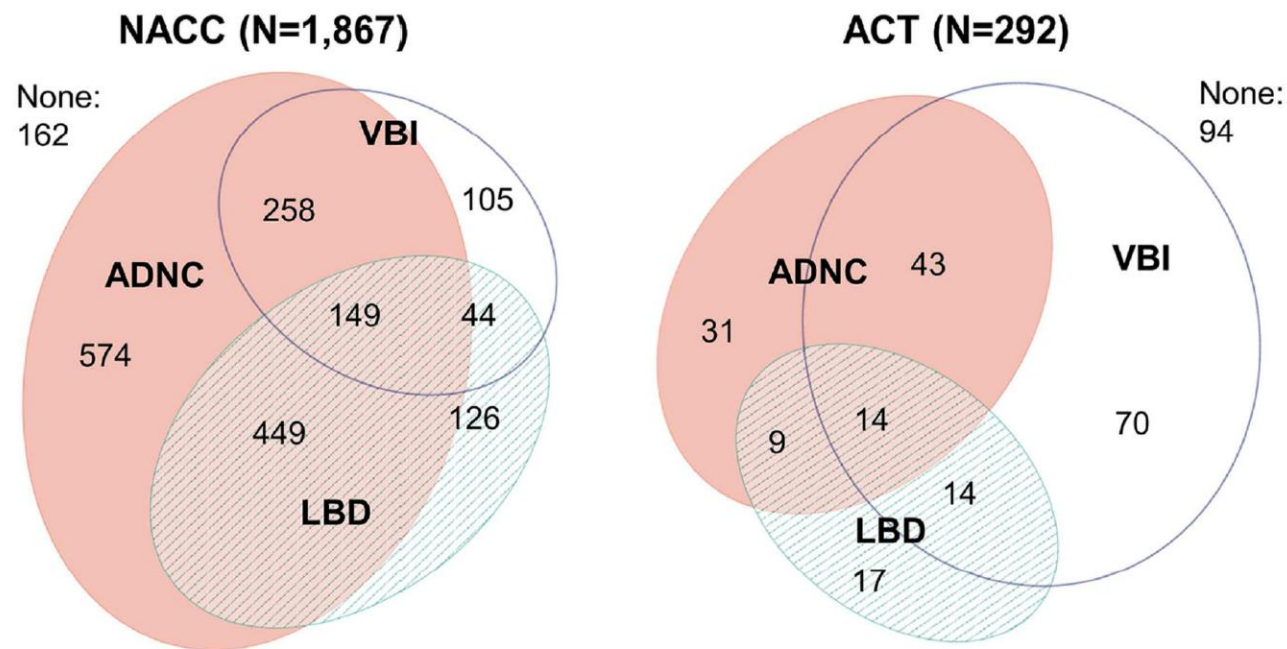
Vascular Dementia
Dementia with Lewy Bodies
Parkinson's Disease Dementia
Frontotemporal Dementia
Huntington's Disease
Creutzfeldt-Jakob Disease
Normal Pressure Hydrocephalus
Traumatic Brain Injury
Down Syndrome Dementia
Korsakoff Syndrome

Alzheimer's
Disease



Alzheimer's disease (AD)

Large autopsy studies show that AD pathologies (ADNP) very often co-occur with vascular brain injury (VBI) and cortical Lewy bodies (LBD). Medial temporal lobe pathologies are also highly co-prevalent (TDP-43, HS, AGD; not shown in the figure).



Epidemiology of AD dementia

Prevalence: 7.4 million in US

>10% of adults age 65+

Increases with age: >35% of adults age 85+

Risk Factors:

Older age

Female sex (2:1)

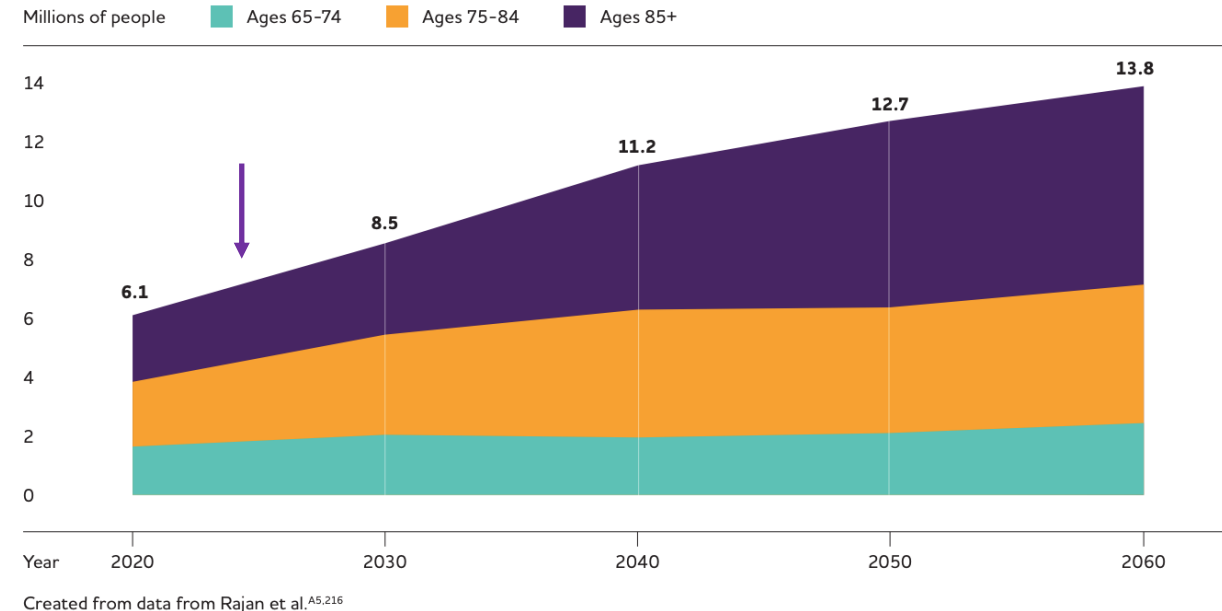
Low socioeconomic status

Vascular risk factors

Neuropsychiatric symptoms (depression, anxiety, apathy)

Genes: apoE4, APP, PSEN1&2

Projected Number of People Age 65 and Older (Total and by Age) in the U.S. Population with Alzheimer's Dementia, 2020 to 2060

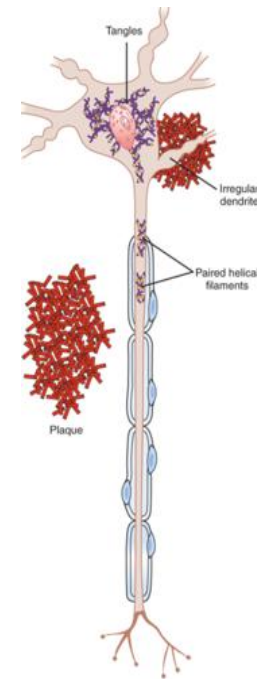
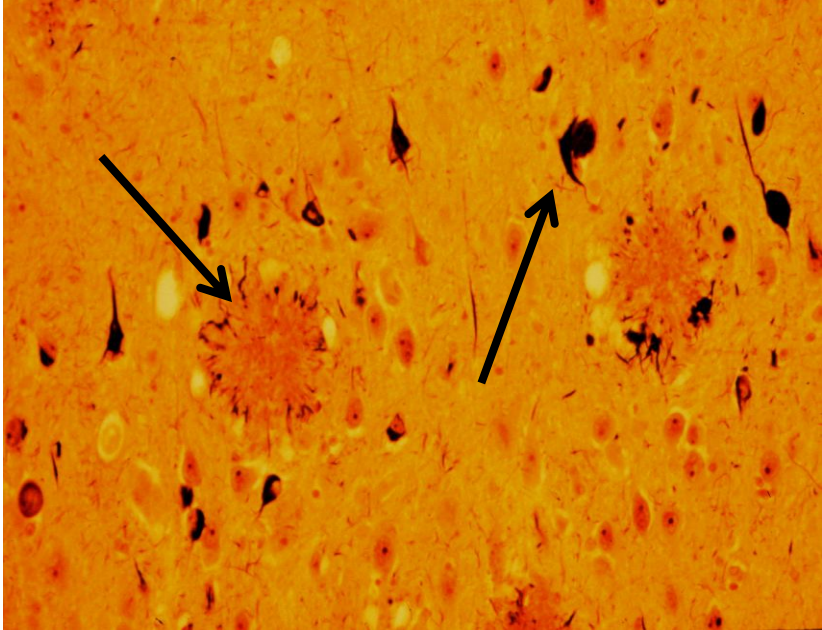


Alzheimer's Association Facts and Figures 2026



Pathobiology of AD

- Extracellular neuritic plaques comprised of amyloid-beta (left) and intracellular neurofibrillary tangles (NFTs) comprised of tau protein (right)
- Downstream neurodegenerative effects: synaptic dysfunction, aberrant neuronal activity, neuronal death, and brain atrophy



ATN Biomarkers of AD

Amyloid biomarker (A+)

- Low CSF A β -42 peptide
- PET: Increased fibrillar A β (greater plaque burden)

Neurodegeneration (N+)

- FDG PET: regional hypometabolism
- MRI: atrophy in medial temporal and basal-lateral temporal regions

Tau biomarkers (T+)

- Elevated CSF total and phosphorylated tau
- PET: increased uptake of paired helical filament tau

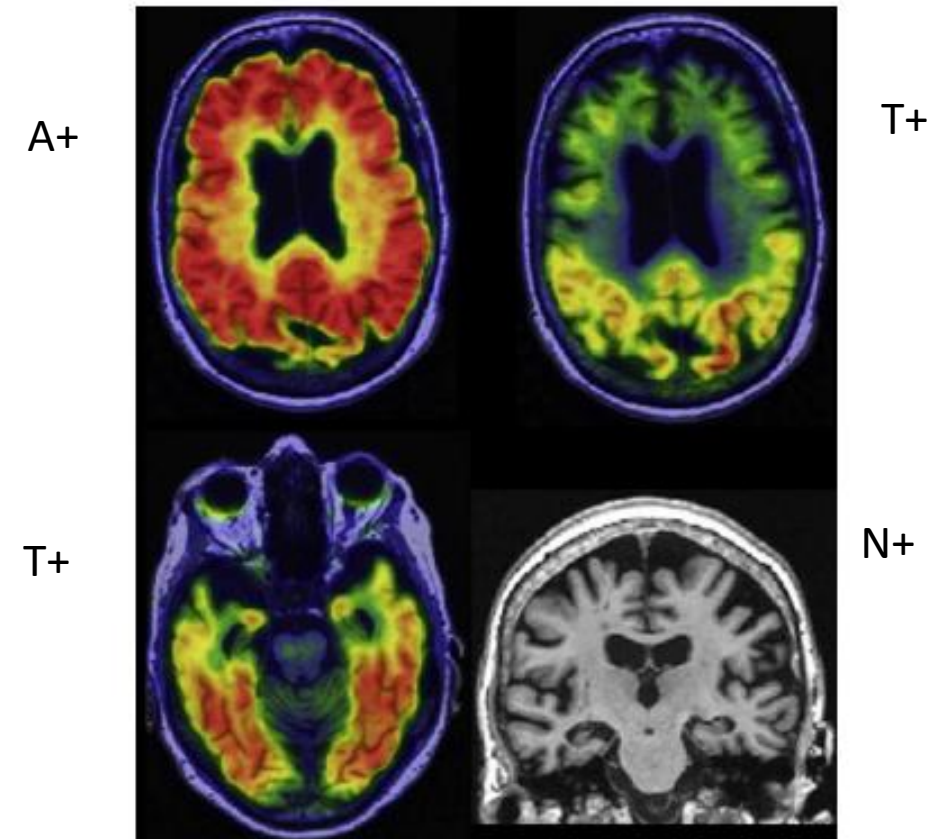
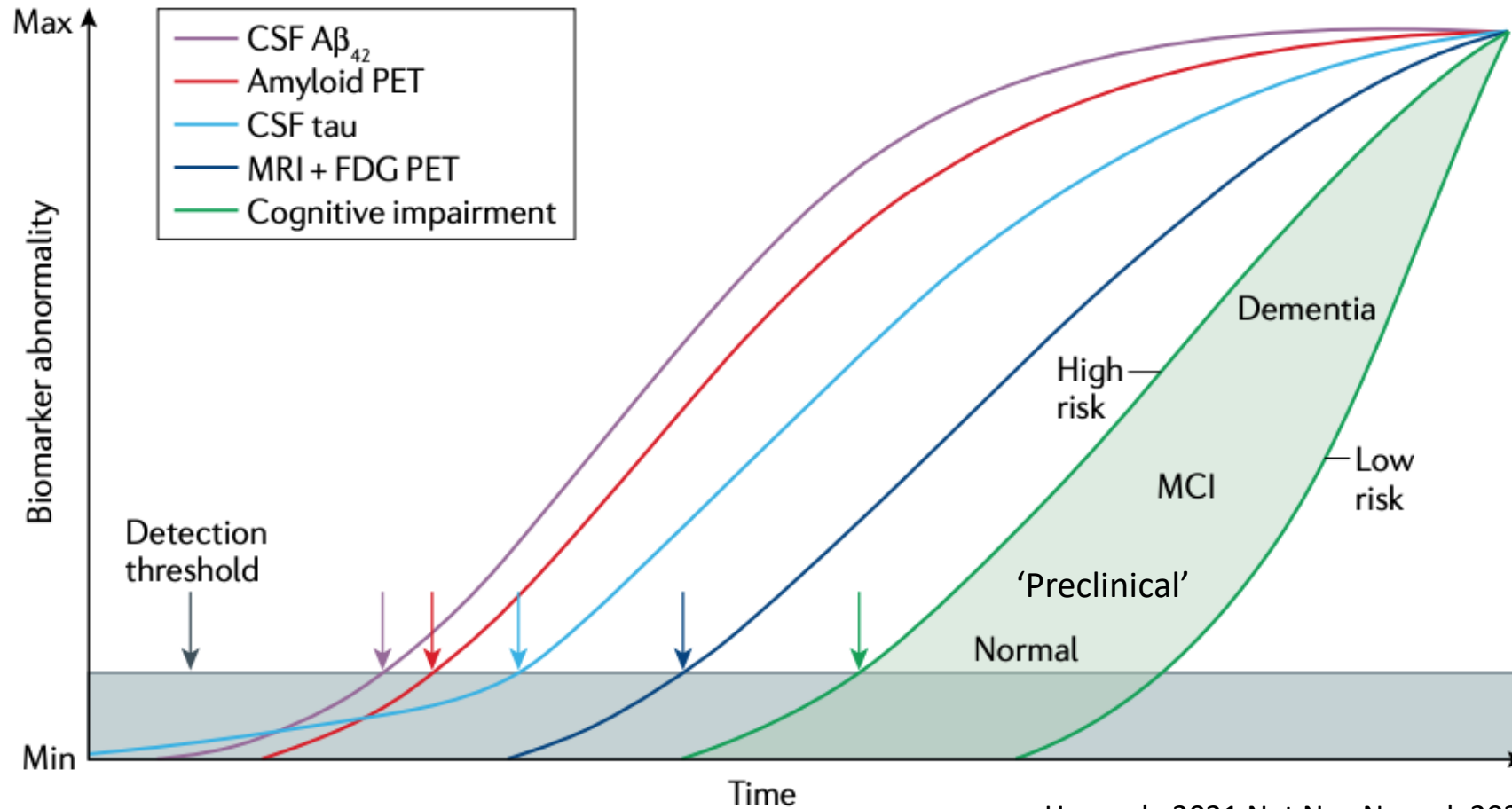


Fig. 1. Alzheimer's disease with dementia. A 75-year-old woman with amnesic multidomain dementia. Participant in the Mayo Alzheimer's Disease Research Center. Abnormal amyloid PET with Pittsburgh compound B (top left), tau PET with flortaucipir (top right and bottom left), and atrophy on MRI (bottom right). Biomarker profile A+T+(N)+.

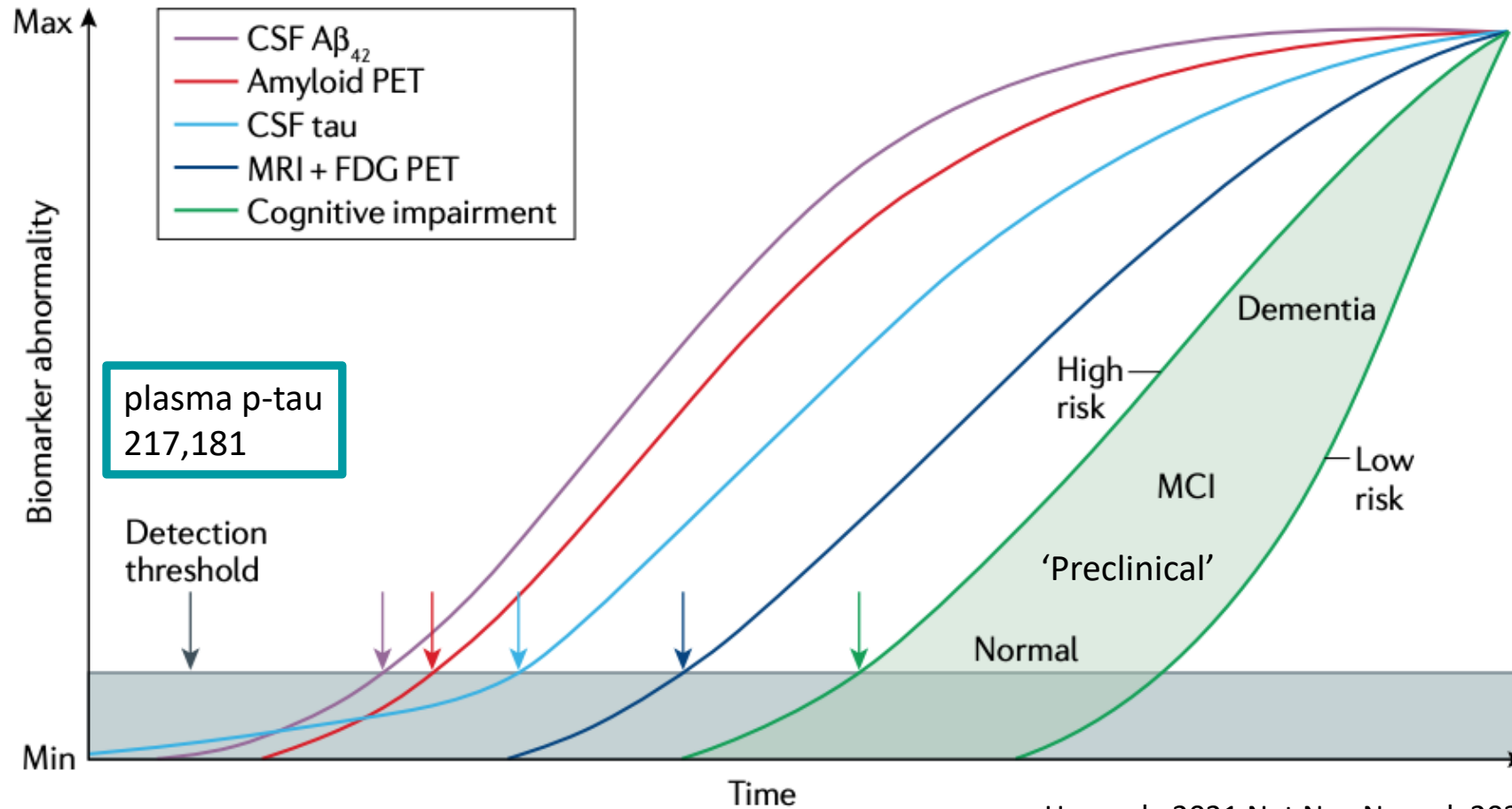
Jack, 2018 Alzheimer's and Dementia 14 (2018) 535-562

Model of AD biomarker changes over time and their relationship to clinical stage



Hampel , 2021 Nat Nev Neurol. 2021 Sep;17(9):580-589

Model of AD biomarker changes over time and their relationship to clinical stage



Hampel , 2021 Nat Nev Neurol. 2021 Sep;17(9):580-589

AD diagnosis, biological and clinical staging

JAMA | Original Investigation

Blood Biomarkers to Detect Alzheimer Disease in Primary Care and Secondary Care

Sebastian Palmqvist, MD, PhD; Pontus Tideman, MSc; Niklas Mattsson-Carlsson, MD, PhD; Suzanne E. Schindler, MD, PhD; Ruben Smith, MD, PhD; Rik Ossenkoppele, PhD; Susanna Callig, MD, PhD; Tim West, PhD; Mark Monane, MD, MBA; Philip B. Verghese, PhD; Joel B. Braunstein, MD, MBA; Kaj Blennow, MD, PhD; Shirena Janelidze, PhD; Erik Stomrud, MD, PhD; Gemma Salvadó, PhD; Oskar Hansson, MD, PhD

Palmqvist, 2024 JAMA doi:10.1001/jama.2024.13855



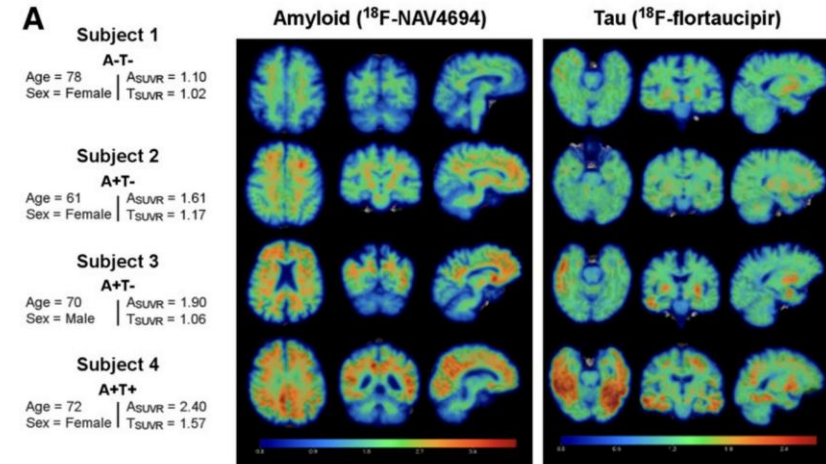
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Groot 2022 J Nuc Med 63(6) 20S-26S

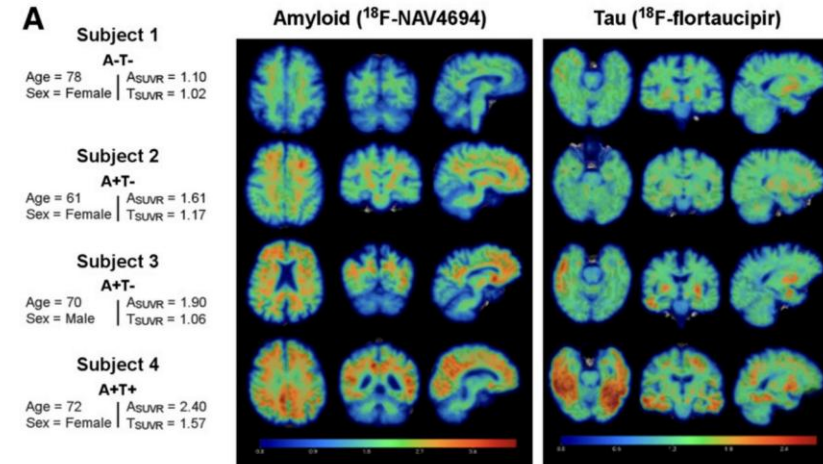
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Palmqvist, 2024 JAMA doi:10.1001/jama.2024.13855



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RESEARCH ARTICLE

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup

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AD diagnosis, biological and clinical staging

TABLE 3 Biological staging.

	Initial-stage biomarkers (A)	Early-stage biomarkers (B)	Intermediate-stage biomarkers (C)	Advanced-stage biomarkers (D)
PET	Amyloid PET A+T ₂ –	Tau PET medial temporal region A+T _{2MTL} +	Tau PET moderate neocortical uptake A+T _{2MOD} +	Tau PET high neocortical uptake A+T _{2HIGH} +
Core 1 fluid	CSF A β 42/40, p-tau181/A β 42, t-tau/A β 42, and accurate ^a Core 1 plasma assays can establish that an individual is in biological stage A or higher, but cannot discriminate between PET stages A–D at present.			



AD diagnosis, biological and clinical staging

TABLE 6 Clinical staging for individuals on the Alzheimer's disease continuum.

'Preclinical AD'	Stage 0 Asymptomatic, deterministic gene^a	No evidence of clinical change. Biomarkers in normal range.
	Stage 1 Asymptomatic, biomarker evidence only	Performance within expected range on objective cognitive tests. No evidence of recent cognitive decline or new symptoms.
	Stage 2 Transitional decline: mild detectable change, but minimal impact on daily function	Normal performance within expected range on objective cognitive tests.
MCI	Stage 3 Cognitive impairment with early functional impact	
Dementia	Stage 4 Dementia with mild functional impairment	Progressive cognitive and mild functional impairment on instrumental ADLs, with independence in basic ADLs.
	Stage 5 Dementia with moderate functional impairment	Progressive cognitive and moderate functional impairment on basic ADLs requiring assistance.
	Stage 6 Dementia with severe functional impairment	



AD diagnosis, biological and clinical staging

TABLE 6 Clinical staging for individuals on the Alzheimer's disease continuum.

'Preclinical AD'	Stage 0 Asymptomatic, deterministic gene^a	No evidence of clinical change. Biomarkers in normal range.	Stage 1: - No evidence of cognitive change - No new symptoms
	Stage 1 Asymptomatic, biomarker evidence only	Performance within expected range on objective cognitive tests. No evidence of recent cognitive decline or new symptoms.	
	Stage 2 Transitional decline: mild detectable change, but minimal impact on daily function	Normal performance within expected range on objective cognitive tests.	
MCI	Stage 3 Cognitive impairment with early functional impact		Stage 2: - Objective cognition: normal range - Incremental cognitive declines or - Subjective cognitive symptoms or - Subtle changes in mood /behavior
Dementia	Stage 4 Dementia with mild functional impairment	Progressive cognitive and mild functional impairment on instrumental ADLs, with independence in basic ADLs.	
	Stage 5 Dementia with moderate functional impairment	Progressive cognitive and moderate functional impairment on basic ADLs requiring assistance.	
	Stage 6 Dementia with severe functional impairment		



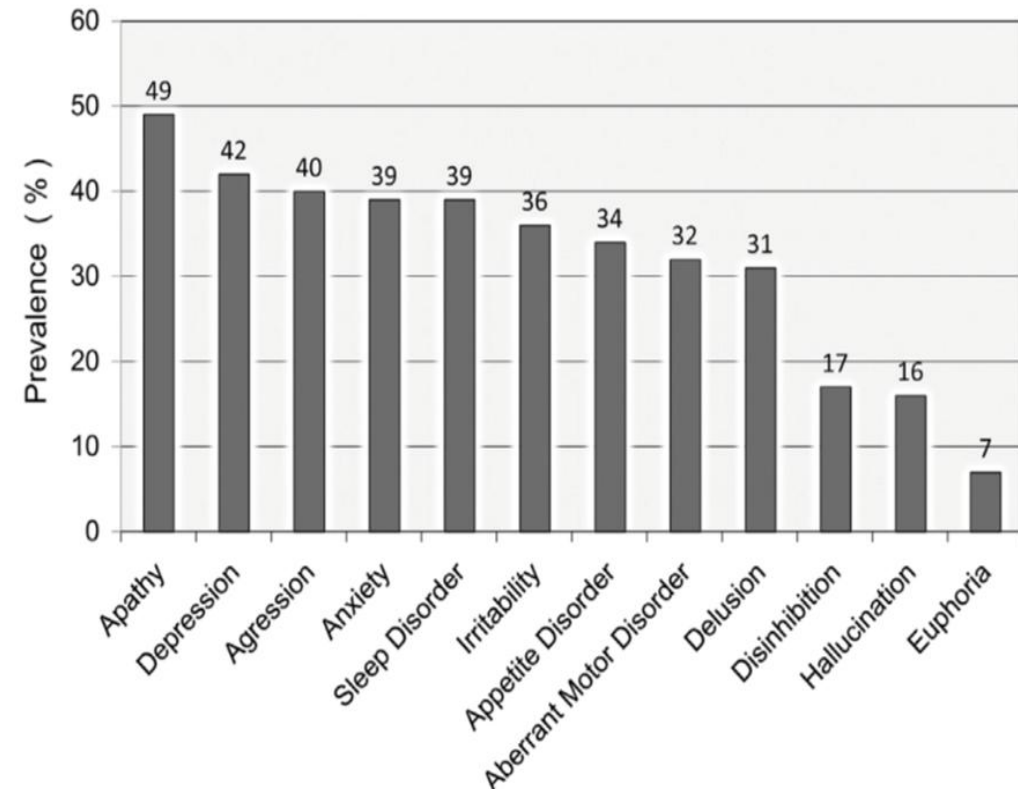
Neuropsychiatric symptoms (NPS) of AD

Point prevalence: 50% in MCI, 75% in dementia stage

Significance:

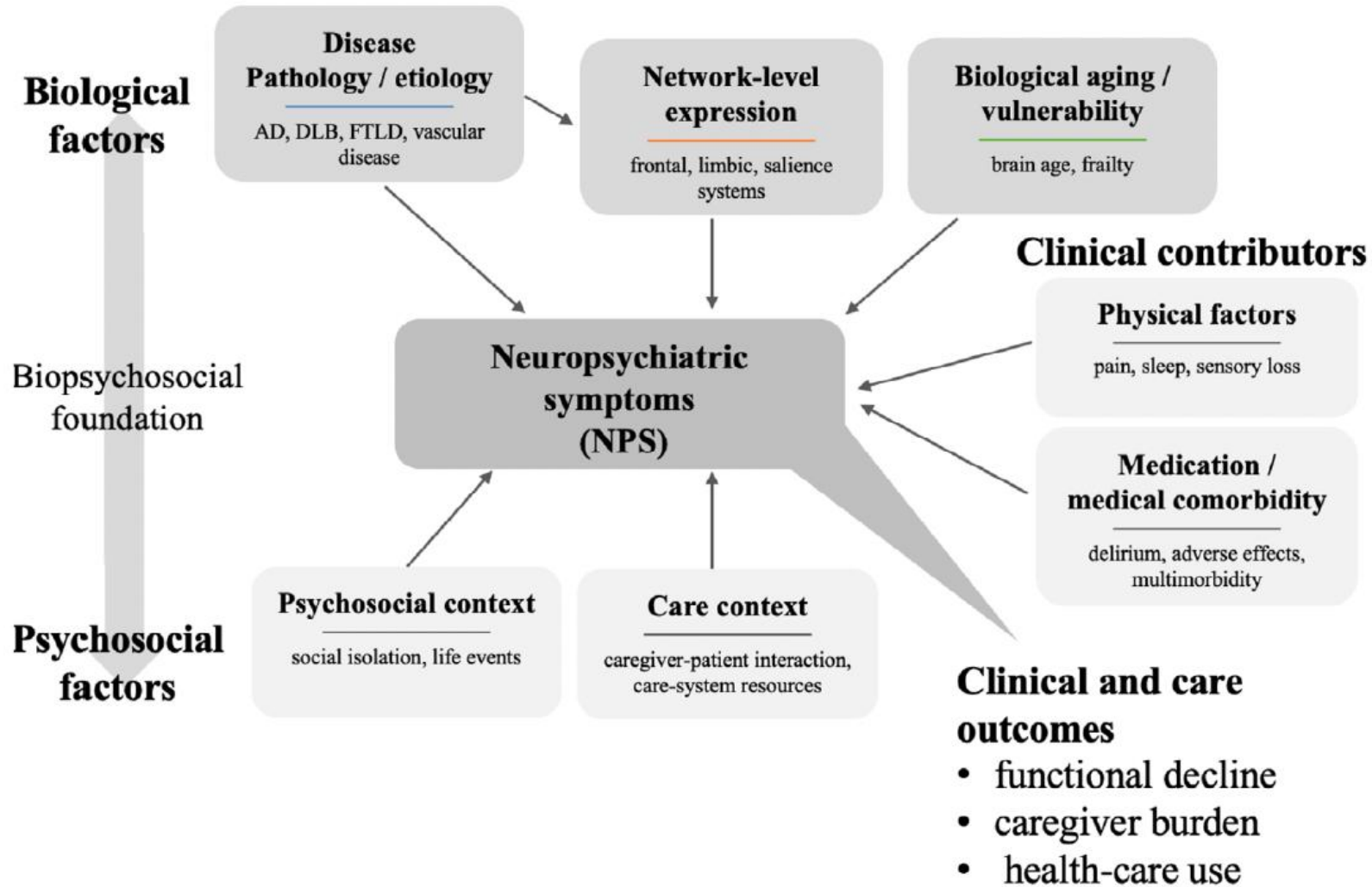
- Decreased patient quality of life
- Caregiver burden
- Increased institutionalization
- Higher health care utilization/costs
- More rapid progression to MCI and dementia stages
- Mortality

Prevalence of NPS at the dementia stage



Zhao, et al. J Affective Disorders, 2016



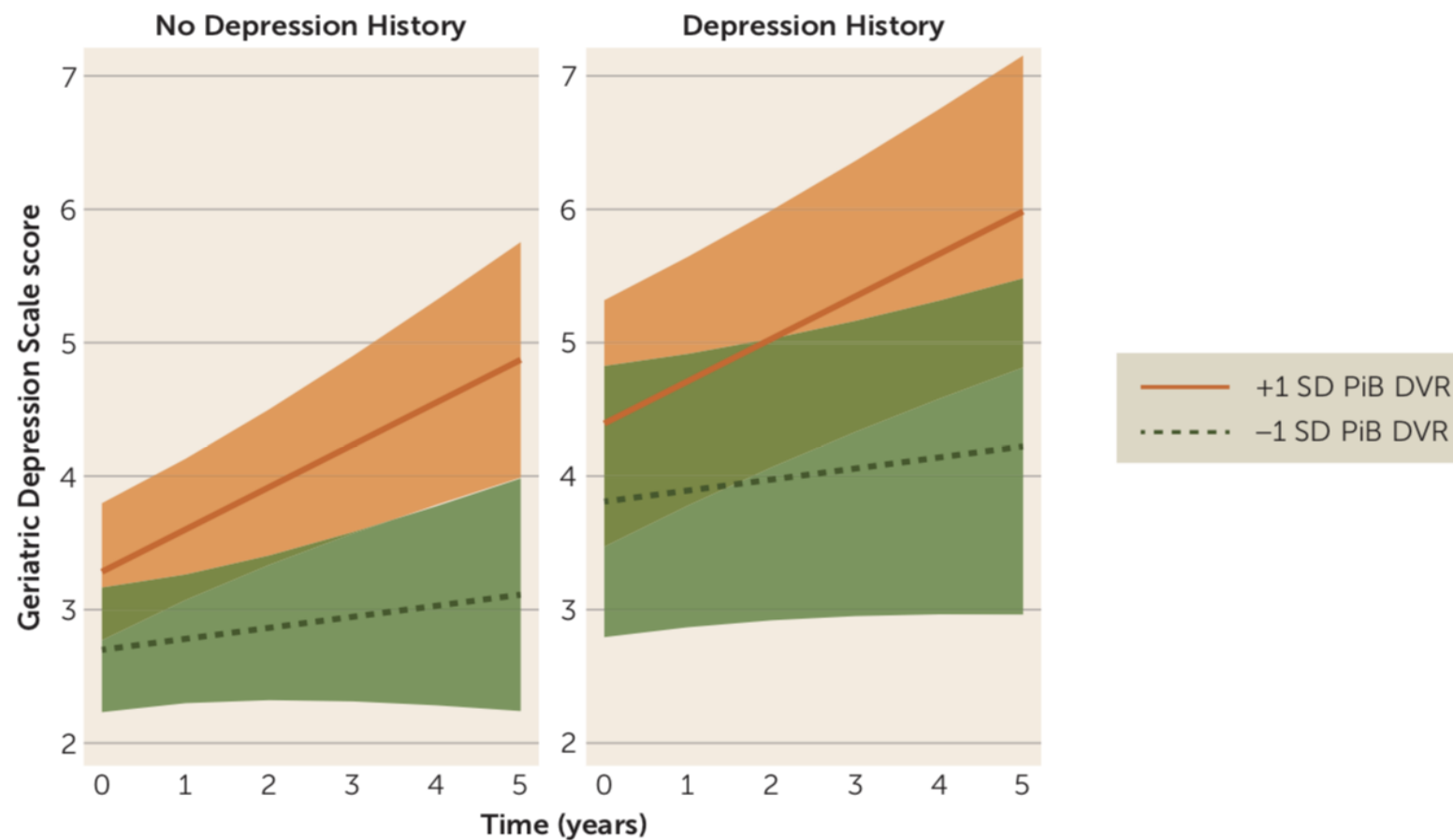


Three hypotheses explaining the role of NPS in AD

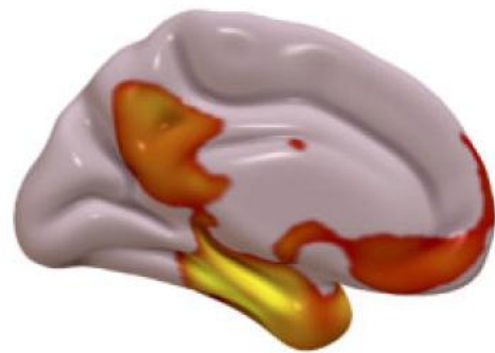
- NPS as clinical manifestations of AD pathology
- NPS as co-morbid factors that interact with and may potentiate progression along the AD pathway
- NPS as emotional or behavioral responses resulting from other AD-related deficits and “unmet needs”



Higher brain amyloid burden was associated with steeper increases in depression in cognitively normal older adults



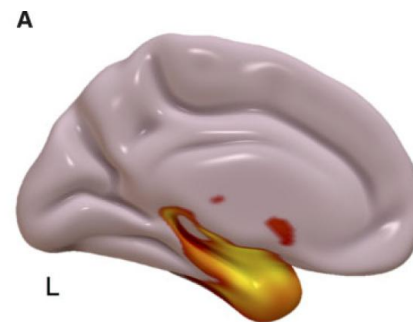
Atrophy network mapping in patients with AD vs controls localizes distinct brain networks for memory and neuropsychiatric symptoms (delusions)



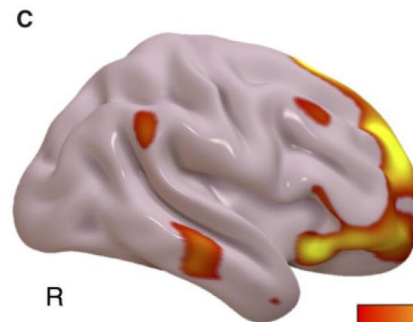
AD vs. Controls

T=4.1 T=9

Comparing group differences
In atrophy network maps

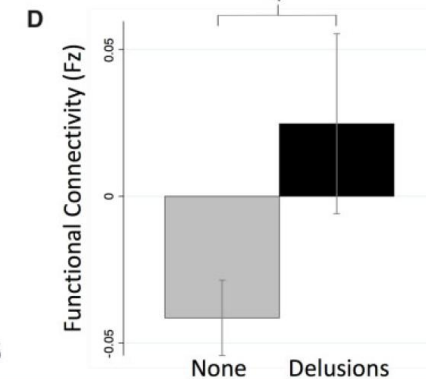
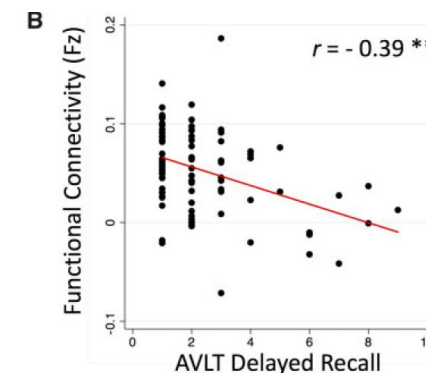


MEMORY



DELUSIONS

T=3.1 T=5

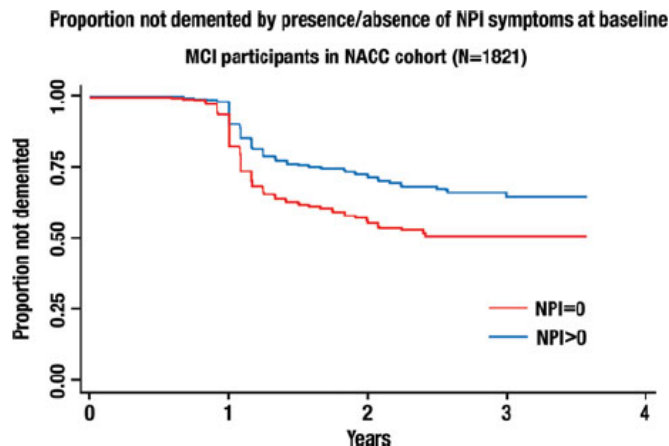


NPS were associated with increased progression from normal cognition to MCI and from MCI to dementia

TABLE 3. Risk of Incident Mild Cognitive Impairment by Baseline Nonpsychotic Neuropsychiatric Symptoms

	Risk Adjusted for Age (Time Scale), Sex, and Education			Risk Additionally Adjusted for Medical Comorbidity		
Amnestic mild cognitive impairment						
Depression	1.75	1.23–2.48	0.002	1.74	1.22–2.47	0.002
Apathy	1.98	1.13–3.47	0.02	1.93	1.09–3.41	0.02
Anxiety	1.65	0.99–2.76	0.05	1.64	0.98–2.74	0.06
Agitation	2.18	1.07–4.44	0.03	2.16	1.06–4.41	0.03
Irritability	1.69	1.09–2.64	0.02	1.69	1.08–2.63	0.02
Appetite/eating	1.09	0.61–1.95	0.78	1.06	0.59–1.91	0.85
Motor disturbance	0.84	0.12–6.01	0.86	0.84	0.12–5.97	0.86
Nighttime behaviors ^a	1.44	0.93–2.24	0.11	1.44	0.93–2.25	0.10

FIGURE 1. Risk of incident dementia stratified by presence/absence of NPI symptoms at baseline.



Any NPS was associated with increased progression to AD dementia (HR 1.35 [1.90-1.66])



Diagnostic Work-up of MCI/Dementia and NPS

History

Collateral information is critical

Symptom onset, time course of progression

Symptom domains involved (cognitive, NPS, neurological, sleep)

Functional impairment (Quick Dementia Rating Scale- useful for staging)

Risk factors (family history, cardiovascular)

Clinical Evaluation

Mental Status Exam

Basic cognitive assessment includes a screening test

(e.g. Montreal Cognitive Assessment (MoCA)) and supplemental tests

(e.g. tests of word fluency, word-list learning tests, tests of naming).

Neuropsychiatric assessment (e.g. NPI-Q, Geriatric Depression Scale)

Neurological Exam

Physical Exam



Diagnostic Work-up of MCI/Dementia and NPS

Laboratory tests

Metabolic panel, CBC, thyroid and liver function, B12, folate

Other specialized tests as indicated

(RPR, HIV, CSF studies for amyloid & tau proteins, plasma p-tau, skin biopsy for alpha synuclein, sleep evaluation)

Other

Formal neuropsychological assessment

Brain imaging

Structural MRI, CT

Additional specialized imaging as indicated (FDG-PET, amyloid imaging)



Neuropsychiatric Inventory (NPI) and brief questionnaire (NPI-Q)

Informant-based measures

Rate 12 neuropsychiatric symptoms over the past month, based on presence, severity, and level of caregiver distress:

- Delusions
- Hallucinations
- Agitation
- Depression
- Anxiety
- Euphoria
- Apathy
- Disinhibition
- Irritability
- Aberrant Motor Behavior
- Sleep disturbance
- Appetite disturbance

Practice guidelines recommend regular screening for NPS in patients with AD at least annually

Cummings et al. 1997 Neurology 48 (5 Suppl 6): S10-16
Kaufer et al. 2000 J Neuropsychiatry 12:233-239



Mild Behavioral Impairment

: Research construct developed by an Alzheimer's Association (ISTAART) work group

Symptoms that have been present for at least 6 months that represent a change from the person's longstanding pattern of behavior

Domains (5)	Examples
Decreased Motivation	Apathy, anhedonia
Affective dysregulation	Depression, anxiety
Impulse dyscontrol	Irritability, agitation, disinhibited behaviors
Social inappropriateness	Loss of social graces, tact and empathy
Abnormal perception or thought	Paranoia, hallucinations
• At least minimal impairment in relationships, work, daily function but independence maintained	
• Not due to psychiatric disorder or medical condition, substance, dementia	

MBI checklist is available online; <http://www.mbitest.org>



Evidence-based treatment for NPS of dementia

Overall principles of treatment

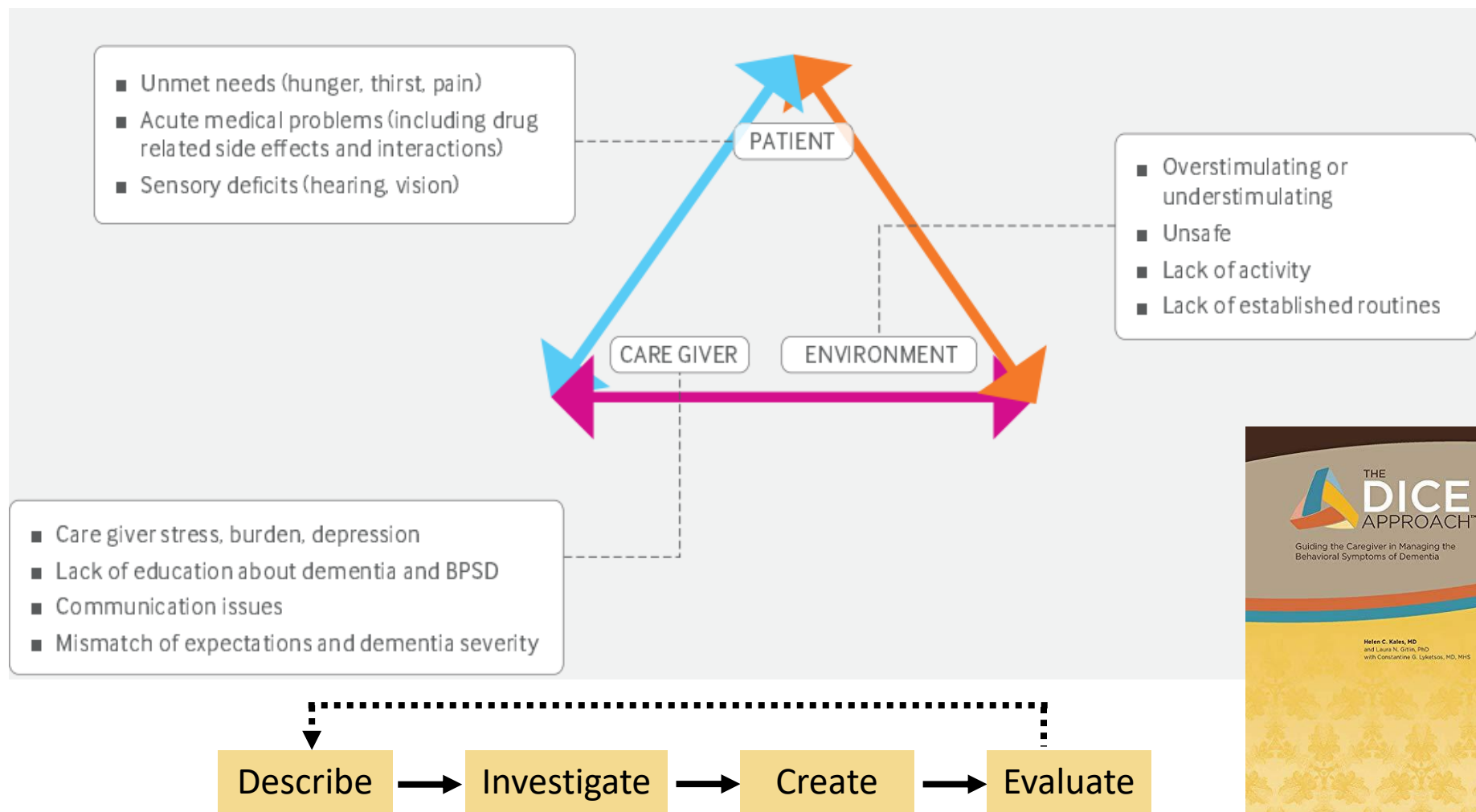
- Develop strategies for both prevention and alleviation of symptoms
- Use non-pharmacological approaches first, especially in non-emergency settings

Basic goals of treatment

- Maximize safety and relieve distress in both patient and caregiver
- Reduce added costs and need for hospitalization/ long term care placement
- Comply with regulatory guidelines for institutionalized patients



The DICE approach



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

Kales HC, Kales HC, Gitlin LN, Lyketsos CG, BMJ 2015;350:h369

<https://diceapproach.com>



Evidence-based treatment for NPS of dementia

Nonpharmacologic Approaches**

Environmental modifications: Structured routines, visual cues, reduce overstimulation (noise, clutter), optimize safety

Gitlin LN et al. JAMA. 2012;308(19):20-9; Rhodus EK et al. Am J Occ Ther 2023 77:4

Pleasant activities with or without social interaction (> 10 min/day) 5 RCT: all showed benefit for agitation; those with social interaction had greater effect

Treating Behavioral and Psychological Symptoms in AD and Dementia Workshop (2013) AAGP Annual Meeting, Los Angeles; Abraha 2017 BMJ Open 7:e012759

Exercise: May reduce depressive symptoms, total NPS and improve sleep. One study found decreased agitation (meta-analysis of 12 RCT of aerobic and strength training)

Williams CL, Tappem RM. Aging Ment Health. 2008;12(1):72-80; Treating Behavioral and Psychological Symptoms in AD and Dementia Workshop (2013) AAGP Annual Meeting, Los Angeles; Abraha 2017 BMJ Open 7:e012759; Kouloutbani et al. Alz Dis Assoc Disord (2023) 37:73-81.



Evidence-based treatment for NPS of dementia

Nonpharmacologic Approaches**

Music therapy: reduction in anxiety, depression, agitation, and aggression

Guétin S et al. Dement Geriatr Cogn Disord. 2009;28(1):36-46, 128. Abraha I, Rimland JM, Trotta FM, et al. BMJ Open. 2017;7(3):e012759. Treating Behavioral and Psychological Symptoms in AD and Dementia Workshop (2013) AAGP Annual Meeting, Los Angeles; Abraha 2017 BMJ Open 7:e012759; Moreno-Morales et al. Front Med 2020: Vol 7/Article 160; Hillebrand et al. IJGP (2023) DOI: 10.1002/gps.5893

Aromatherapy: with and without (hand) massage improved scores on NPI and agitation/CMAI (meta-analysis 15 RTC, 821 patients).

Wang et al, 2024 JAMDA 105199

Cognitive stimulation therapy: aims to stabilize and improve cognitive impairment, also found to reduce apathy, depression, and overall severity of NPS

Niu YX, Clin Rehabil. 2010;24(12):1102-11.

Reminiscence:

12 RCT, 7/8 studies showed benefit for depression (no consistent findings on agitation, QOL)

Treating Behavioral and Psychological Symptoms in AD and Dementia Workshop (2013) AAGP Annual Meeting, Los Angeles; Abraha 2017 BMJ Open 7:e012759



Evidence-based treatment for NPS of dementia

Nonpharmacologic Approaches**

Indoor daylight exposure:

2 hours of socialization in perimeter room with daylight exposure (8-10 AM) in 4 LTC versus control (socialization in interior room)
Lower depression in the daylight exposure group.

Bright light therapy (RTC):

Morning and evening bright light vs. typical indoor light
Active group showed greater agitation/aggression compared to baseline. A RCT of Blue LED phototherapy vs conventional light found improved sleep quality (actigraphy, PSQI) and overall NPS ratings

Konis et al. Clin Interv Aging 2018; 13:1071-1077

Dowling et al. Wes J Nurs Res 2007; 29:961-75

Jao 2022 Innov Aging; Mar 24 (6)3

Chen et al. 2023 Gerontology

Aini et al. 2024 AJGP 32(6) 681-706



Ecopsychosocial treatments for dementia-related NPS

Group engagement in persons with dementia : addresses need for social contact and alleviate boredom:

- Reading, singing, baking, creative story-telling, brain games, active games, exercise, holiday discussion- each group session was conducted twice in randomized order.

Montessori Programming for Dementia (MPD)

Use of Montessori materials adapted for use in dementia:

Designed to promote new learning and positive forms of engagement either constructive (verbal or physical interaction) or passive (watching) .

- Advanced dementia patients showed more engagement and pleasure using this program

Across studies: games, singing, catching a ball, kneading dough or baking- beneficial effects on mood and measures of engagement

Ziesel et al, 2016 AJ Alz Dis Other Disorder 31(6):502-7;

Cohen-Mansfield et al. 2017 Psych Res 2017; 251:237-242

Camp 2010 Nonpharmacol Ther Dement. 1(2):163-174



Evidence-based treatment for NPS of dementia

Pharmacologic Approaches**

Prior to 2023, there was no FDA approved medication for the management of neuropsychiatric symptoms in Alzheimer's dementia.

- Risperidone has approval in Europe and Canada for persistent **agitation** in moderate to severe Alzheimer's disease.
- Brexpiprazole (Rexulti) approved for **agitation** in AD dementia in 2023.
- Dextromethorphan-bupropion (Auvelity) approved for **agitation** in AD dementia in 2026

Guidance:

American Psychiatric Association Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients with Dementia (2016)

Evidence base:

Depression in dementia

Apathy in dementia

Agitation in dementia

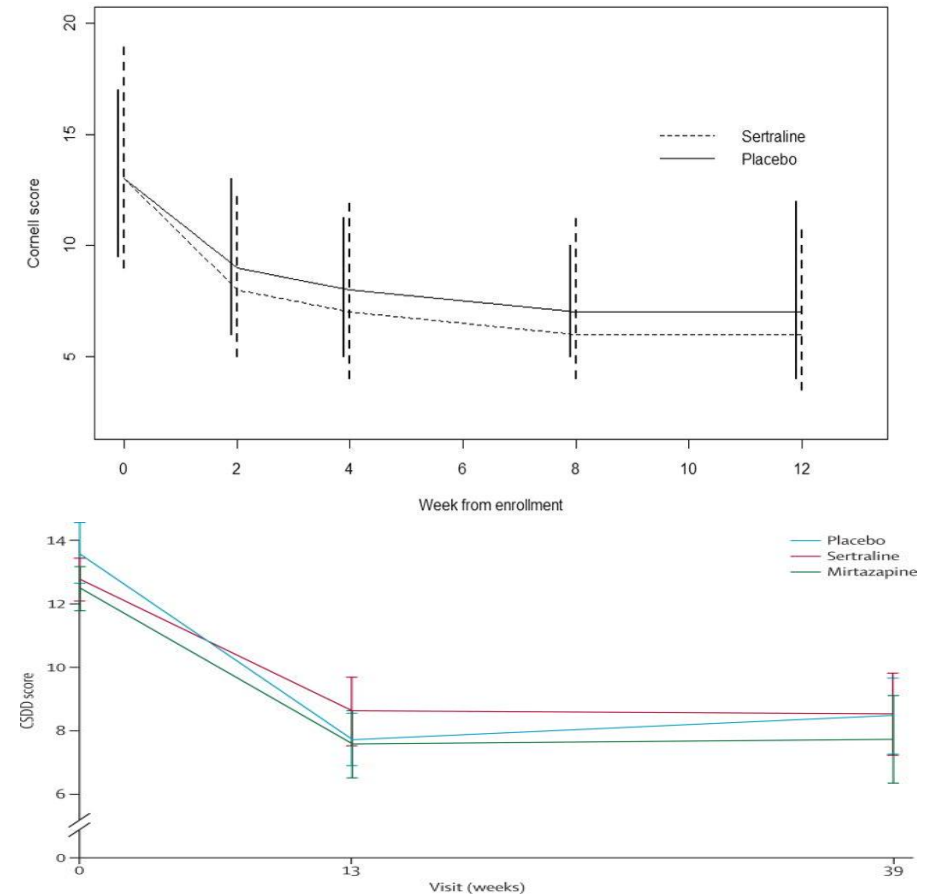
Sleep disturbance in dementia



Evidence-based treatment for NPS of dementia

Pharmacologic Approaches for Depression

- DIADS II study: No difference in depression scores between Sertraline and placebo treated subjects with dementia at 12 or 24 weeks
- Changes in depression with Sertraline, Mirtazapine or placebo were equivalent in elderly subjects with dementia ([HTA-SADD](#))



Rosenberg 2010 AJGP 18(2):136-45; Weintraub 2010 AJGP 18(4): 332-34;
Banerjee et al. 2011 Lancet 378 (9789) 403 - 411



Evidence-based treatment for NPS of dementia

Pharmacologic Approaches for Depression

- Past meta-analysis of RCTs showed no significant benefit of Sertraline, Mirtazapine, Fluoxetine and TCA's (Imipramine and Clomipramine) compared to placebo

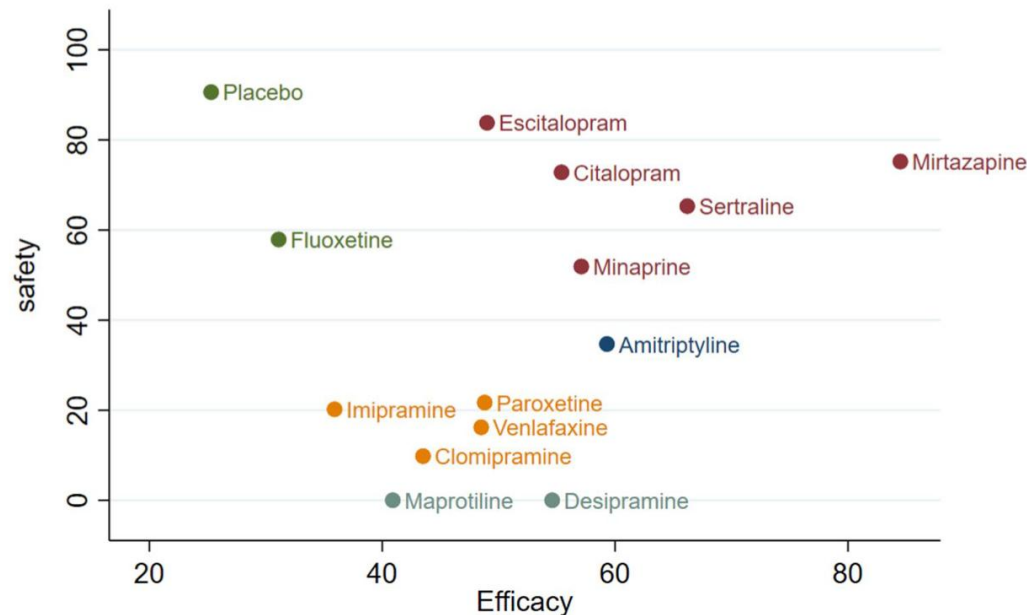
Orgeta V, Tabet N, Nilforooshan R, Howard R. J Alzheimers Dis. 2017;58(3):725-33.



Evidence-based treatment for NPS of dementia

Pharmacologic Approaches for Depression

- Meta-analysis included 25 RCT (n=2137) for antidepressant treatment of depression in AD
- **Sertraline (9 trials) and Mirtazapine (2 trials) were found to be slightly effective and safe (AEs equivalent to placebo).**
- Network meta-analysis indicated that **Sertraline, Escitalopram, Citalopram and Mirtazapine formed a cluster with similar efficacy and safety.**



Fluoxetine –equivalent to placebo in efficacy and safety.

Most TCAs , paroxetine and venlafaxine were less safe and less effective than the top group.



Evidence-based treatment for NPS of dementia

Pharmacologic Approaches for Apathy

Summary of consensus definition of apathy in cognitive disorders

- At least two of the 3 signs, present for at least 4 weeks and represents a change.
 - a. Diminished initiative (e.g., hobbies, chores, self-care, social activities)
 - b. Diminished interest (e.g., environment, others, friends and family)
 - c. Decreased emotional expression or responsiveness (less affection, empathy)
- Behaviors cause excess disability in interpersonal relationships, social functioning, or in the ability to perform or participate in daily activities
- Is not due to another psychiatric disorder, disabilities, decreased level of consciousness or effects of a substance.

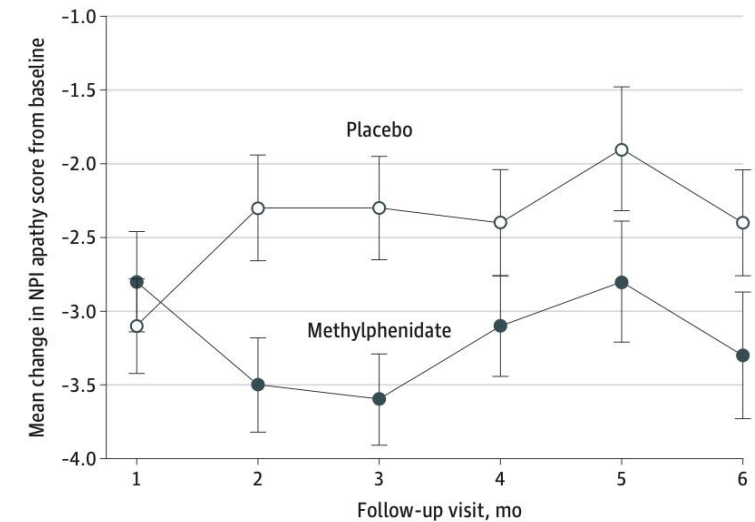


Evidence-based treatment for NPS of dementia

Pharmacologic Approaches for Apathy

ADMET II study - Methylphenidate:

- 200 participants with AD dementia and apathy were randomized to placebo or Methylphenidate 10 mg twice daily
- Larger decrease in NPI apathy subscale for the active treatment and a higher hazard of having no apathy at follow up
- No group difference in other outcomes : Most other NPI domains, cognition, QoL or safety profile
- But a higher NPI aberrant motor behavior rating in the methylphenidate group



Mintzer et al. 2021 JAMA Neurol 78(11): 1324-1332

Clark et al. 2023 Alz Dementia TRCI 9:e12403 38



Evidence-based treatment for NPS of dementia

Pharmacologic Approaches for Agitation and Psychosis

Summary of consensus definition of agitation in cognitive disorders

- At least one of the following signs of emotional distress, present for at least 2 weeks
 - a. **Excessive motor activity** (e.g., pacing, rocking, repetitious behaviors)
 - b. **Verbal aggression** (e.g., profanity, screaming, shouting)
 - c. **Physical aggression**
- Behaviors cause excess disability in interpersonal relationships, social functioning, or in the ability to perform or participate in daily activities
- Agitation is not due to another psychiatric disorder, suboptimal care, medical condition or effects of a substance.

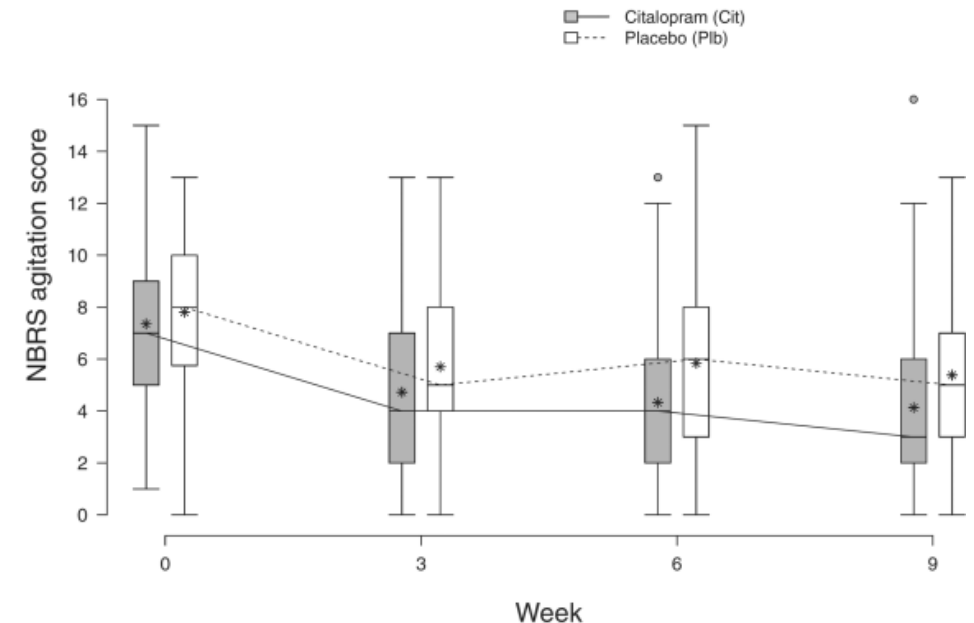


Evidence-based treatment for NPS of dementia

Pharmacologic Approaches for Agitation

Antidepressants: Citalopram

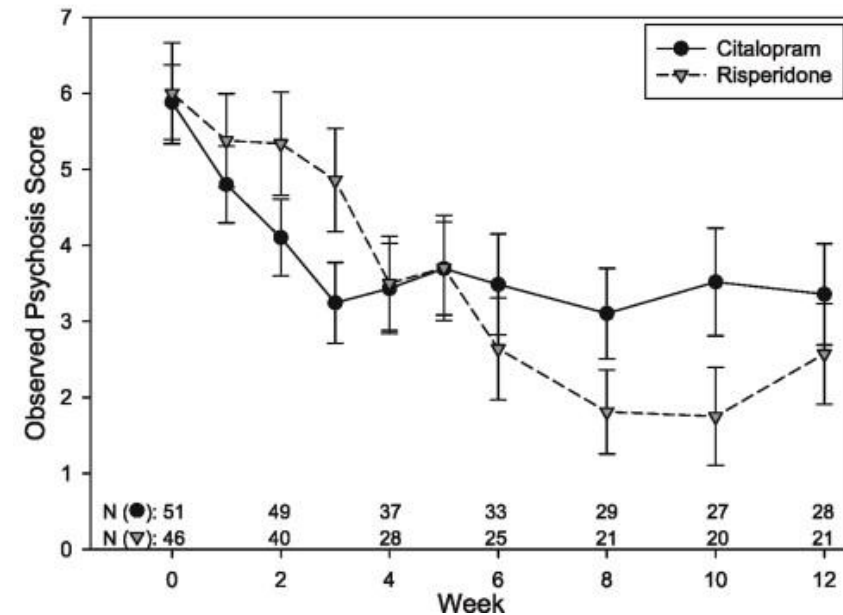
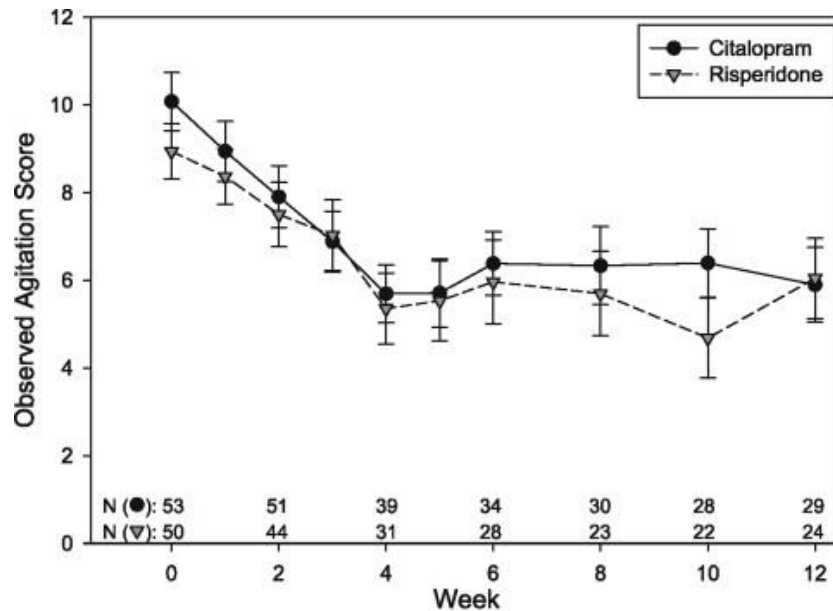
- CitAD (double-blind RCT (n= 186))
 - Randomized to a psychosocial intervention +/- Citalopram titrated to 30 mg
 - **Significant reduction in agitation, total NPI score, and reduction in caregiver distress.**
 - Citalopram-associated with QTc prolongation and 1 point decline on MMSE, more respiratory tract infections and falls
 - Secondary analyses- reduced odds of experiencing anxiety, irritability and delusions- sizable clinical effect
 - Current recommended maximum daily dose: 20 mg



Evidence-based treatment for NPS of dementia

Pharmacologic Approaches for Agitation and Psychosis

- Citalopram was equivalent to Risperidone for treatment of agitation and psychosis in dementia diagnosed as AD, VaD, mixed, DLB or Dementia NOS.

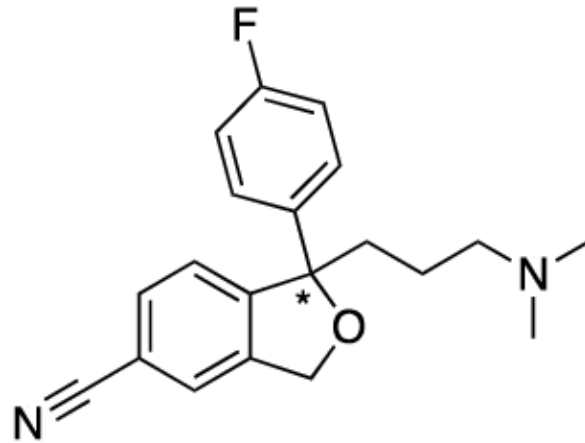


Evidence-based treatment for NPS of dementia

Pharmacologic Approaches for Agitation

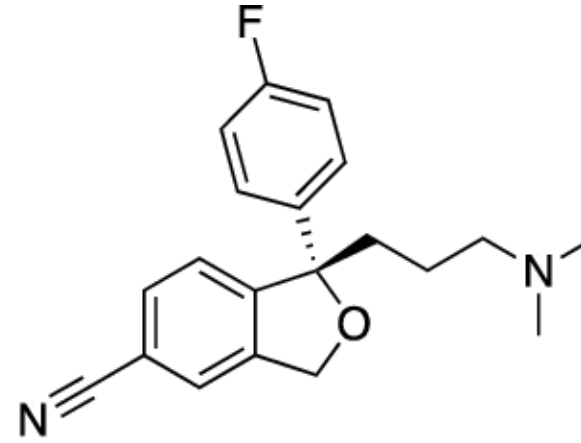
Antidepressants: Citalopram and Escitalopram

- QTc Prolongation and cognitive decline were related to R-enantiomer, while treatment efficacy was related to S-enantiomer



Citalopram

Racemic mixture of R- and S-enantiomers of citalopram



Escitalopram

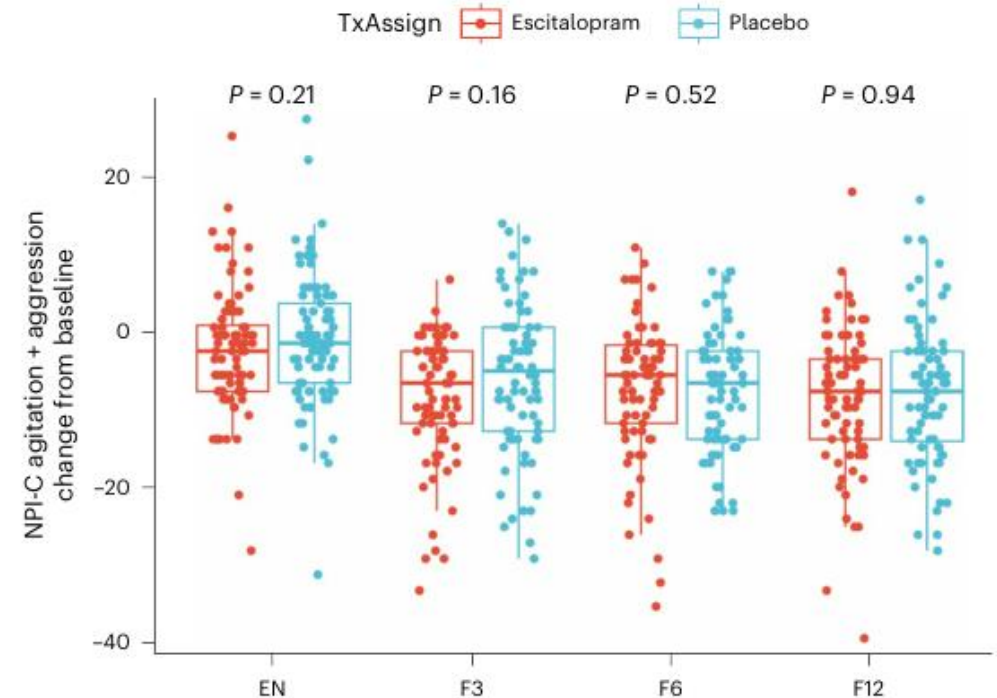
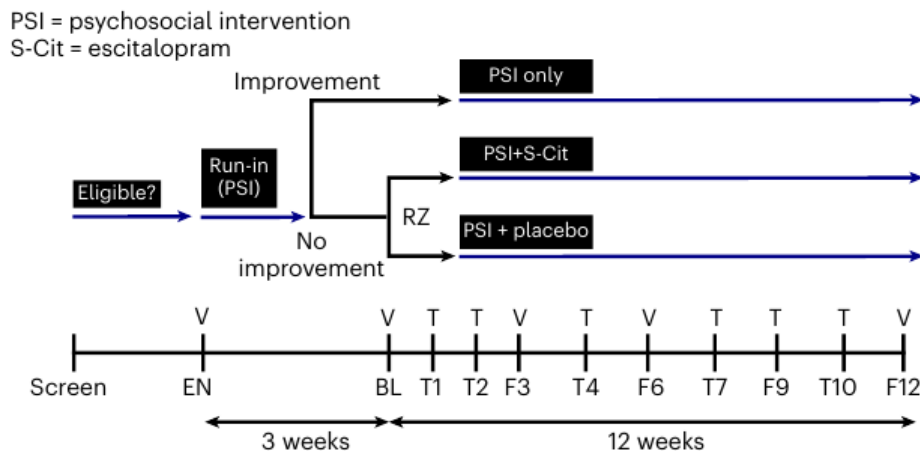
S-enantiomer of citalopram only

Evidence-based treatment for NPS of dementia

Pharmacologic Approaches for Agitation

Antidepressants: Escitalopram

- Double-blind RCT in AD dementia (n= 173); *target n=392*
- Psychosocial intervention (PSI) non-responders were randomized to placebo or Escitalopram (ES) up to 15 mg
- **12 weeks: there was mod to marked improvement in agitation in 27% placebo, 34.5% ES, NS difference.**
- More falls and QT prolongation in ES group vs placebo.
- No difference in cognition SAEs; anxiety lower in ES.



- This study was not fully enrolled /fully powered.
- Failed to demonstrate efficacy of Escitalopram for agitation in patients who failed PSI
- Though difficult to draw conclusions, has led to speculation that Citalopram may be preferable to Escitalopram.



Evidence-based treatment for NPS of dementia

Pharmacologic Approaches for Agitation

- **Antipsychotics (summary):**
 - **Risperidone**, moderate evidence for efficacy, large evidence base; small effect size. Superior to placebo for treatment of agitation in meta-analysis; 1-2 mg/day studied
 - **Aripiprazole**, moderate evidence for efficacy. Reduction in agitation; small effect size; 2-15 mg /day studied
 - **Brexpiprazole**, FDA approved based on prior 12-week RCT. 2 and 3 mg per day superior to placebo; small effect size.
 - **Olanzapine**, weak evidence for efficacy, large evidence base. Meta-analysis of numerous large studies DID NOT show significant reduction in agitation; 2.5-10 mg /day
 - **Quetiapine**, weak evidence for use, no significant reduction in agitation in three meta-analyses. 50-200 mg/day. Lowest risk of mortality
 - **Haloperidol**, effective in reducing aggression, but highest risk for mortality



Risperidone

reduces agitation and aggression in dementia

: 6 RCT on balance have shown modest but significant improvement in these symptoms

: Behave AD study* - 625 nursing home patients over 12 weeks, 0.5, 1 or 2 mg/day

- Improvement at 1 mg/day, greater effect at 2 mg/day versus placebo
- Incidence of EPS was 13% at 1 mg, 21% at 2 mg

Study	Sample	Dose	Design	Outcome	Duration	Results
Brodsky 2003, 2005	AD, VaD, mixed, MMSE<24 N=345	Flexible 0.5-2 mg Mean 1 mg/day	Placebo RCT	Agitation Psychosis	Nursing home 12 weeks	Risperidone >Placebo agitation psychosis
Deberdt 2005	AD, VaD, mixed N=494 (196)	Flexible 0.5-2 mg Mean 1 mg	Placebo RCT Olanzapine	Agitation Psychosis	Outpatient, Residential 10 weeks	Risperidone =placebo agitation psychosis
DeDyn 1999	MMSE<24 N=344	Flexible 0.5-4 mg Mean 1 mg	Placebo RCT Haloperidol	Agitation	Hospital, Institution 12 weeks	Risperidone >Placebo agitation
Katz 1999*	AD, VaD, mixed, MMSE<24 N=625	Fixed 0.5, 1, or 2 mg/day	Placebo RCT	Agitation Psychosis	Nursing home 12 weeks	Risperidone >Placebo agitation =placebo psychosis
Mintzer 2006	AD MMSE 5-23 N=473	Flexible 0.5-1.5 mg Mean dose 1 mg/day	Placebo RCT	Agitation Psychosis	Nursing home 10 weeks	Risperidone =placebo agitation psychosis
Schneider 2006	AD MMSE 5-26 N=421	Flexible Mean 1 mg/day	Placebo RCT Olanzapine (mean 5.5mg/day) Quetiapine (mean 56.5 mg/day)	Time to discontinuation	Community or Assisted living Mean 7 weeks	Risperidone =placebo
Sultzer 2008				Hostility Psychosis Agitation		Risperidone >Placebo



Aripiprazole

has been shown to reduce agitation in AD dementia in 10-week placebo-controlled trials

: Dose range 2-15 mg, optimal dose may be 10 mg

Study	Sample	Dose	Design	Outcome	Duration	Results
Breder 2004 Mintzer 2007	MMSE 6-22 N=284/487	Fixed 2, 5, 10 mg	Placebo RCT	Agitation Psychosis	Nursing home 10 weeks	Aripiprazole >Placebo agitation psychosis
De Deyn 2005	AD N=208	Flexible 2-15 mg; mean 10 mg	Placebo RCT	Psychosis	Outpatients	Aripiprazole =placebo psychosis >Placebo Agitation; total NPI, BPRS
Streim 2008	AD N=151/256	0.7-15 mg Mean 9 mg	Placebo RCT	Agitation Psychosis	Nursing home 10 weeks	Aripiprazole =placebo Psychosis >placebo Agitation
Rappaport 2009	Dementia AD, VaD, Mixed D.	Fixed 5, 10, or 15 IM in two 2hr apart injections; 24 follow-up	Placebo RCT	Agitation	Healthcare facilities	Aripiprazole>Placebo Pos-Neg symptoms; agitation



Brexipiprazole

FDA approved for agitation in AD dementia

Three 12-week placebo controlled RCT showed significant improvement in agitation at 2 or 3 mg per day

Sample	Dose	Design	Outcome	Duration	Results
AD MMSE 5-22 N= 433 NPI>=4 agitation or aggression	Fixed 1, 2 mg placebo	Multicenter randomized double-blind, placebo controlled	CMAI total score 2 nd CGI severity of agitation; NPI-Agit; Aggression	12 weeks	2 mg group: significant improvement in CMAI at 12 week Cohen's d -0.25
AD MMSE 5-22 N=270 NPI>=4 agitation or aggression	Flexible 0.5-2 mg	Multicenter randomized double-blind, placebo controlled	CMAI Score 2 nd CGI severity of agitation; NPI-Agit; Aggression	12 weeks	Group titrated to 2 mg at week 4 showed CMAI reductions Cohen's d - 0.41 And greater improvement in CGI-S Cohen's d -0.59; & NPI scores.
Probable AD MMSE 5-22 N= 345 NPI>=4 agitation or aggression	Fixed 2-3mg Placebo	Multicenter randomized double-blind, placebo controlled	CMAI total score 2 nd CGI severity of agitation Safety	12 weeks	CMAI reductions Cohen's d -0.35 CGI-S-S Cohen's d -0.31 Generally well tolerated over 12 weeks

Post-hoc analyses of clinical trial data also showed reduced NPI irritability/lability, anxiety, aberrant motor behavior & caregiver distress with Brexpiprazole



Grossberg et al. AJGP 2020 28(4): 383-400; Lee et al. JAMA Neurol 2023;80;(12):1307-1316

Grossberg et al. JGerPsych Neurol 2025 0(0)1-13

Brexipiprazole

FDA approved for agitation in AD dementia

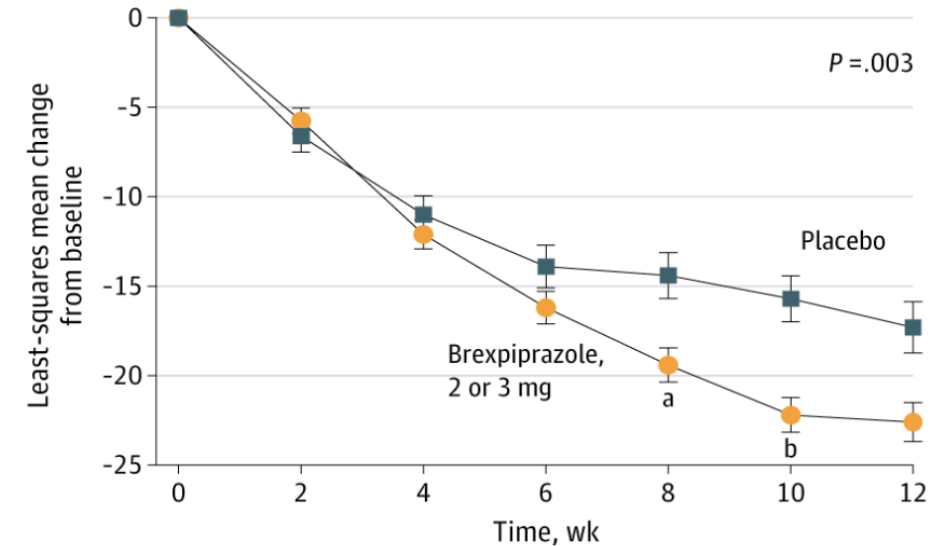
Side effects :

- Headache (m/c) - Brexpiprazole [6.6%] vs placebo [6.9%]
Other - dizziness, urinary tract infection, nasopharyngitis and somnolence/sedation, minimal EPS
- 1 death in the Brexpiprazole group - unrelated to treatment
- Retains black box warning for class: increased risk of death for dementia patients (Prior RCT : 5 deaths, all unrelated to treatment)

Recommended dosing:

- 0.5 mg per day for 7 days; 1 mg per day for 7 days; then 2 mg per day (target dose)
- After 14 days on 2 mg can be increased to maximum dose 3 mg per day based on clinical response and tolerability (see full prescribing information)

CMAI total score



* CMAI : Cohen-Mansfield Agitation Inventory



Olanzapine

Evidence for the use of Olanzapine for agitation and psychosis in dementia is weak

: A meta-analysis that included 5 placebo-controlled trials concluded that olanzapine was not associated with efficacy overall.

Study	Sample	Dose	Design	Outcome	Duration	Results
Deberdt 2005	AD, VaD, mixed N=494; 204 Olanzapine	Flexible 2.5-10 mg Mean 5 mg	Placebo RCT	Agitation Psychosis	Outpatient, Residential 10 weeks	Olanzapine =placebo agitation psychosis
DeDyn 2004	AD MMSE 5-26 N=652	Fixed 2.5, 5, 7.5 mg	Placebo RCT	Agitation Psychosis	Longterm Care 10 weeks	Olanzapine =placebo agitation psychosis
Street 2000	AD N=206	Fixed 5, 10, 15 mg	Placebo RCT	Agitation Psychosis	Nursing home 6 weeks	Olanzapine >placebo agitation = placebo psychosis
Schneider 2006, Sultzer 2008	AD MMSE 5-26 N=421; 100 Olanzapine	Flexible Mean 5.5 mg/day	Placebo RCT Risperidone Quetiapine	Time to discontinuation	Community or Assisted living Mean 7 weeks	Olanzapine =placebo
				Hostility Psychosis		Olanzapine >placebo hostility



Quetiapine

was found to be ineffective for agitation in dementia

Study	Sample	Dose	Design	Outcome	Duration	Results
Ballard 2005	AD N=93; 26 Quetiapine	50 mg BID	Placebo RCT Rivastigmine;	Agitation	Nursing home 26 weeks	Quetiapine =Placebo Agitation; Greater cognitive decline
Paleacu 2008	ADMMSE <24 N=40	Flexible 50-300 mg Mean 200 mg	Placebo RCT Olanzapine	Agitation CGI-C	6 weeks	Quetiapine =placebo agitation Quetiapine >placebo CGI-C
Schneider 2006, Sultzer 2008	AD MMSE 5-26 N=421; 85 Quetiapine	Flexible Mean 56 mg/day	Placebo RCT Olanzapine Risperidone	Time to discontinuation	Community or Assisted living Mean 7 weeks	Quetiapine=placebo
				Hostility Psychosis		Quetiapine=placebo
Tariot 2006	AD N=284	Flexible Mean 96 mg/day	Placebo RCT Haloperidol	Agitation Psychosis	Nursing home 10 weeks	Quetiapine=placebo agitation psychosis
Zhong 2007	AD or Vascular D N=333	Fixed titration 100-200 mg/day	Placebo RTC	Agitation Psychosis	Nursing home 10 weeks	Quetiapine=placebo agitation psychosis



Concerns for the use of antipsychotics for agitation in dementia : class effects

- EPS, sedation, gait disturbance and falls
- Increased respiratory and urinary tract infections.
- Increased cognitive decline
- Increased risk of cerebrovascular events
- Increased mortality risk (OR 1.7) for people with AD treated with antipsychotics versus placebo in RTCs. Rates were 4.5% versus 2.6%. Highest mortality risk with Haloperidol.

ALL antipsychotics carry a black box warning of higher risk of mortality and cerebrovascular events in elderly patients with dementia.



Evidence supports the continued use of antipsychotics (> 6 months) in a subset of patients with severe NPS, agitation and psychosis.

While the Dementia antipsychotic withdrawal trial (DART-AD) study found no benefit for antipsychotics vs. placebo after 6 months in the sample as a whole:

- Those with NPI >15 showed did show significantly lower agitation after 6 months with continued treatment.

A randomized double-blind trial of continuation treatment of 112 AD patients in LTC with risperidone vs. placebo found:

A greater relapse rate (agitation and psychosis) for placebo (48%) vs. risperidone (15%), HR 4.88 $p=0.02$; AEs did not differ.

Ballard et al 2008 PLoS Med ; 5(4)e76; Ballard et al 2009 Lancet Neurol; 8:151-57
Devanand et al 2012 NJEM 367;16: 1497-1507
Declercq et al. Cochrane Database Syst Rev 2013



Dextromethorphan-bupropion (Auvelity)

FDA approved for agitation in AD dementia (2026)

Prior approval as antidepressant for Major Depressive Disorder: NMDA receptor antagonism and sigma 1 receptor agonism plus bupropion effects with CYP2D6 inhibition

Trial	Design	Number of participants	Primary end point	Outcome	Statistics/effect
ADVANCE-1	Double-blind randomized; AXS-05 versus placebo versus bupropion (5 weeks)	366	Change in CMAI agitation score	Positive	−15.4 versus −11.5 placebo; <i>P</i> =0.010
ADVANCE-2	Randomized placebo controlled (5 weeks)	408	Change in CMAI	Mixed/negative	13.8 versus 12.6 point reduction on CMAI, <i>P</i> =NS
ACCORD-1	Randomized withdrawal relapse-prevention 24 weeks	178	Time to relapse	Positive	HR ≈ 0.275; <i>P</i> =0.014; relapse 7.5% versus 25.9%
ACCORD-2	Randomized withdrawal relapse prevention	167	Time to relapse	Positive	HR ≈ 0.276; <i>P</i> =0.001; relapse 8.4% versus 28.6%

CMAI, Cohen Mansfield Agitation Inventory; HR, Hazard ratio; NS, not significant.

As reviewed by Ballard 2026 Nat Rev Neurol

Please see full prescriber information

Dextromethorphan-quinidine reduced agitation in a RCT of 194 subjects with AD; clinical trials ongoing
Cummings 2015 JAMA 314(12):1242-1254



Review of other clinical trials for agitation

- **Anticonvulsants**
 - Carbamazepine: 2 small, 6 wk RTC for AD agitation/aggression showed possible benefit.
 - Valproate: has not been effective in individual studies or meta-analysis
- **Lithium**
 - A single RCT (n=77; 58 completers) found no difference in NPI agitation/aggression for LiCO₃ (150-600 mg daily) vs placebo over 12 weeks. Li was well-tolerated. Larger trial advised.
- **Cholinesterase Inhibitors**
 - have not been effective for agitation over 12 weeks.
 - meta-analysis of 17 RCT found that CIs improved NPI ratings of hallucinations and delusions in AD and Parkinson's disease patients over 10-24 weeks; very small effect sizes.
- **NMDA receptor antagonist**
 - Possible benefit of Memantine for neuropsychiatric symptoms over 3-6 months (but not for acute agitation) based on meta-analyses and pooled data.
- **Mirtazapine**
 - RTC (n=204). No difference over 12 weeks in agitation for Mirtazapine vs placebo with a potentially higher mortality in the Mirtazapine group.



Evidence for other agents for agitation

Prazosin (up to 6 mg/day) reduced agitation at 8 wk RTC. 22 subjects with AD.

Pimavanserin reduced psychosis in 12 wk RTC in AD (n=181) and, in responders, agitation.

- In AD or other dementia psychoses, continuation lowered psychosis relapse risk compared with discontinuation.

Cannabinoids (THC, dronabinol, nabilone) – Prior meta-analysis of 6 small RTCs- mixed results; More recent RCT showed positive results:

- Nabilone was associated with reduced agitation, total NPI and caregiver distress in a 14-week crossover RTC (n=39).
- Dronabinol titrated to 5 mg twice daily over 3 weeks was superior to placebo for AD-related agitation with a moderate effect size in a RCT (n=75). There was increased somnolence in the Dronabinol group

ECT – A systematic review and meta-analysis of 13 studies (206 patients) found that ECT led to rapid & robust improvement in agitation/aggression (78% response) and onset within 3 sessions. AEs mostly mild and transient with no persistent severe complications.



Evidence-based treatment for NPS of dementia

Pharmacologic Approaches for sleep disturbance

- **Trazodone:** one small RCT (total N=30) showed significant increase in time asleep in trazodone group, at dose of 50 mg nightly
- **Suvorexant (10-20 mg) or Lemborexant (5-10 mg):** orexin antagonists; Suvorexant label was updated in 2020 to include clinical trial data in AD patients (n=285) showing safety and improved total sleep and disruptions.
- **Melatonin, ramelteon:** systematic review found no evidence of benefit or harm in the use of either.
- **Mirtazapine:** A small RCT showed no significant improvement in nocturnal sleep; did show increase in daytime sleepiness
- **Benzodiazepines** generally avoided, associated with cognitive impairment, delirium, falls, fractures and motor vehicle accidents in older adults



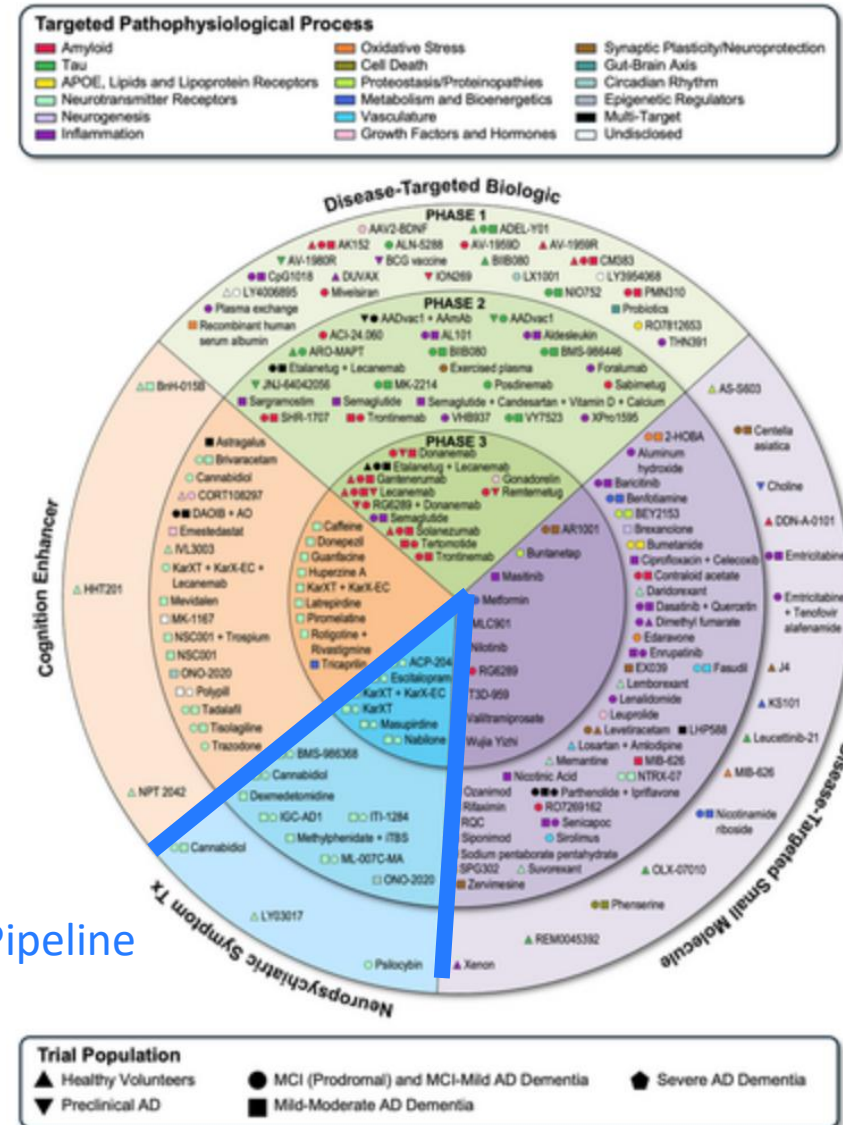
Areas of investigation:

- **Vortioxetine:** antidepressant binds multiple 5HT receptors; 5HT3 antagonism enhances release of 5HT, NE and Ach (possible pro-cognitive effect). Open label study of 115 clinic patients with MCI and mild AD dementia showed overall improvements in GDS, NPI and MMSE. A 6-week RCT of 110 patients with AD dementia and depression found no differences of drug vs. placebo in depression or cognition over 12 weeks.
- **Xanomeline-Tropium Chloride (Cobenfy):** Dual M1/M4 muscarinic receptor agonist with no direct D2 dopamine blocking activity has been FDA approved for treatment of psychosis in schizophrenia. Two Phase 3 programs are studying its use in AD dementia with hallucinations/delusions and with agitation/aggression.



Treatment trials for NPS

- Drugs aiming to ameliorate neuropsychiatric symptoms in participants with AD are shown in blue
- Phase 3 Drugs Targeting NPS (2026)
 - ACP-204 – Selective 5-HT_{2A} receptor antagonist/inverse agonist for psychosis (Acadia)
 - Dextromethorphan + Bupropion – NMDA receptor antagonists (with sigma-1 receptor agonism) for agitation
 - Dextromethorphan + Quinidine – Sigma-1 receptor agonist + NMDA receptor antagonists for agitation
 - Escitalopram – SSRI for agitation
 - Nabilone – Synthetic cannabinoid for agitation



Summary

- Neuropsychiatric symptoms are core features of Alzheimer's disease including the preclinical stage.
- Expert guidelines and research emphasize standardized approaches to assessment of these symptoms. Engagement in social and pleasurable activities is important for people with dementia, even with advanced disease.
- Citalopram and certain atypical antipsychotics such as Risperidone have been shown to modestly improve agitation in dementia. Brexpiprazol and Dextromethorphan-bupropion are FDA approved for agitation in AD. Increasing evidence supports the use of cannabinoids (Nabilone and Dronabinol) and ECT for agitation.
- Pharmacological interventions for agitation are most appropriate for patients with high neuropsychiatric symptom burden and symptoms unresponsive to non-pharmacological strategies.





Thank you for your attention



Mass General Brigham