#CHAIR2017

# 10TH ANNUAL CHAIR SUMMIT

neuroscience CME

Master Class for Neuroscience Professional Development

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# Major Neurocognitive Disorder: The Beginning and the End.

## *Making the Diagnosis and Addressing Distressing Behavior*

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## Disclosures


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- ***Consultant:*** Multiple Energy Technologies; Anthem Insurance

# Learning Objective 1

Review the importance of early detection and intervention in Alzheimer's disease (AD).

# Learning Objective 2

Integrate emerging tools and biomarker assessments into the diagnosis and treatment of AD.

# Learning Objective 3

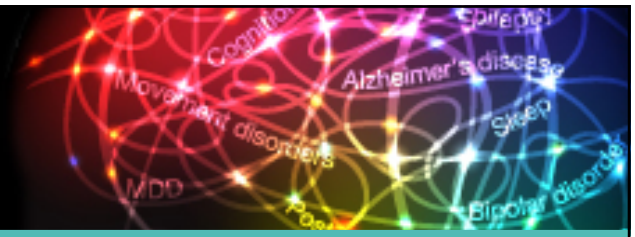
Evaluate emerging data on the efficacy and safety of agents for AD, including agents in development for treating cognitive and behavioral complications associated with AD.

# *DSM-5* Terminology: An Update


- Delirium
- Major neurocognitive disorder
- Minor neurocognitive disorder
- Replaces DSM-IV "Delirium, Dementia and Amnestic and Other Cognitive Disorders"

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. American Psychiatric Publishing. 5th ed. 2013.

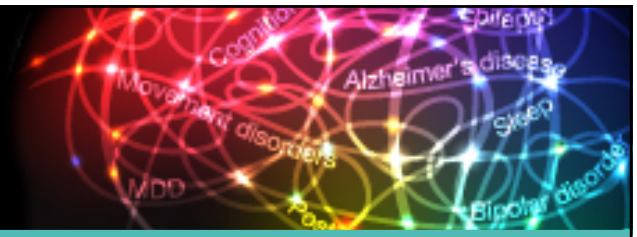
# *DSM-5* Cognitive Domains




- Complex attention
  - Sustained and divided attention, processing speed
- Executive ability
  - Planning/ decision making
- Learning and memory
  - Immediate and recent recall, free recall, cued recall and recognition
- Language
  - Expressive and receptive
- Visuoconstructional-perceptual activity
  - Construction and visual perception
- Social cognition
  - Emotions and behavioral regulation

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. American Psychiatric Publishing. 5th ed. 2013.

# *DSM-5* Delirium




- Disturbance in attention and awareness
- Develops over short period of time, and tends to fluctuate in severity during the day
- An additional cognitive domain disturbance
- Physiologic consequence of a medical condition, substance intoxication or withdrawal, toxin exposure, or multiple etiologies

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. American Psychiatric Publishing. 5th ed. 2013.

# Major Neurocognitive Disorder (A Syndrome) Including What Was Formerly Known as Dementia

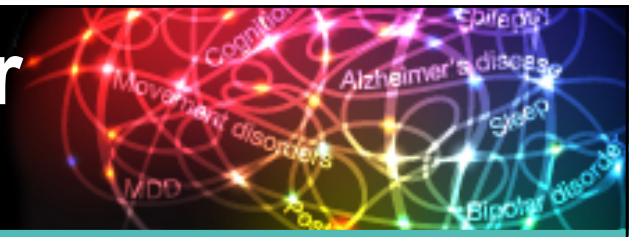
A. Evidence of "significant" cognitive decline in one or more cognitive domains
   1. "Significant" cognitive decline noted by patient, informant, or clinician
   2. Objective evidence of "substantial" impaired cognition, preferably by standard neuropsychological testing

B. Cognitive deficits interfere with independence in everyday activities

C. Cognitive deficits do not occur exclusively in context of delirium

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. American Psychiatric Publishing. 5th ed. 2013.

# Major Neurocognitive Disorder Due to Alzheimer's Disease



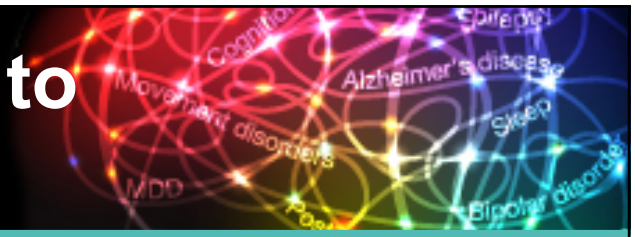

A. Criteria met for major neurocognitive disorder (MND)*

B. Insidious onset and gradual progression of impairment in one or more cognitive domains

*Mild MND, difficulty with instrumental activities of daily living; Moderate MND, difficulty with basic activities of daily living; Severe MND = dependent on others.

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. American Psychiatric Publishing. 5th ed. 2013.

# Major Neurocognitive Disorder Due to Alzheimer's Disease (cont'd)

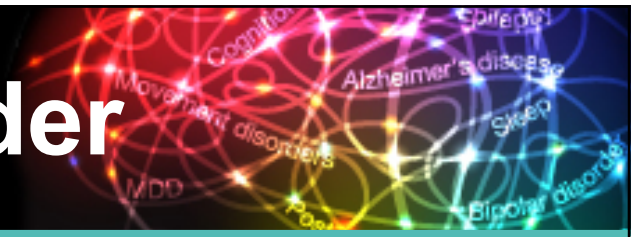



C. Criteria met for probable AD:
   1. Either: Evidence of a causative AD genetic mutation
      - < 1% of all AD
   2. Or: All three of the following:
      - Decline in memory and learning plus at least one other cognitive domain
      - Steady, gradual decline without "extended" plateaus
      - No evidence of mixed etiology

D. Not better explained by cardiovascular disease, another neurodegenerative disorder, or another mental, neurologic, or systemic disorder

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. American Psychiatric Publishing. 5th ed. 2013.

# Mild Neurocognitive Disorder




- Previous referred to as MCI
- Evidence of "modest" cognitive decline in one or more cognitive domains
  - "Mild" cognitive decline noted by individual, caregiver, or provider
  - "Modest" impairment documented, preferably by standard neuropsychologic testing
  - Cognitive deficits do not interfere with capacity for independence in everyday activities
  - Cognitive deficits do not occur exclusively in context of delirium

MCI = mild cognitive impairment.

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. American Psychiatric Publishing. 5th ed. 2013.

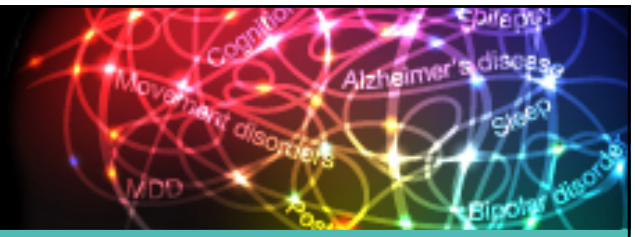
# The Office-Based Assessment of Neurocognitive Disorder


- A careful history from a family member/reliable informant
- Quantify cognitive function, e.g., MMSE, MOCA, SLUMS
- ADL screening (Barthel Inventory or Katz ADL Scale)
- Screening neurological exam
- Laboratory (CMP, CBC, TSH, B12/Folate); UA (RPR, HIV testing, if indicated); some also recommend: Vitamin D level; CRP; homocysteine level.
- MRI or CT (old stroke, tumor, NPH, frontotemporal atrophy)
- Complete neuropsychological testing (if available)
- Repeat cognitive assessment in six-to-twelve months to confirm/clarify diagnosis, measure disease trajectory
- Importance of early recognition

TSH = thyroid stimulating hormone, CBC = complete blood count, BUN = blood urea nitrogen, LFT = liver function test, CMP = complete metabolic profile, UA = urinalysis, RPR = Rapid Plasma Reagin, CRP = c-reactive protein, NPH = normal pressure hydrocephalus, MMSE = mini mental state exam, MOCA = Montreal Cognitive Assessment, SLUMS = St Louis University Mental Status Evaluation.

Weiner MF, Lipton AM. *Clinical Manual of Alzheimer Disease and Other Dementias*. Arlington, VA: American Psychiatric Press; 2012.

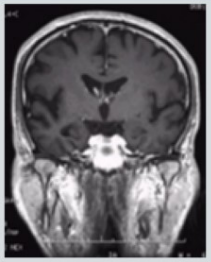
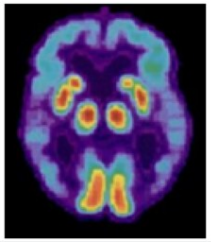
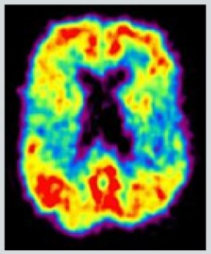
# Biomarkers in AD




- Focus shifted to the identification of AD and treatment in the early clinical stages, as well as before cognitive symptoms emerge during the long preclinical stage
- Neurodegeneration in AD is estimated to start 20 to 30 years before the first clinical symptoms become apparent.
- An early diagnosis with reliable biomarkers is essential to distinguish between mild AD, and other dementia types
- Can serve as a guide for treatment

Sutphen CL, et al. *Biol Psychiatry*. 2014;75(7):520-526.

# Neuroimaging in AD

| Study | | AD Marker Examined |
|---|---|---|
| MRI |  | • Structural changes (eg, atrophy, hippocampal volume), and vascular changes<br>• Functional changes in hippocampal activation and neuronal degeneration |
| FDG-PET |  | • Measures cerebral glucose transport and temporoparietal hypometabolism<br>• Metabolic patterns of uptake can discriminate between normal cognition, MCI, and clinical AD |
| Amyloid PET |  | • Detects cerebral Aβ accumulation<br>• Significant Aβ accumulation predicts risk of cognitive decline<br>• Diagnostic for AD-related dementia |

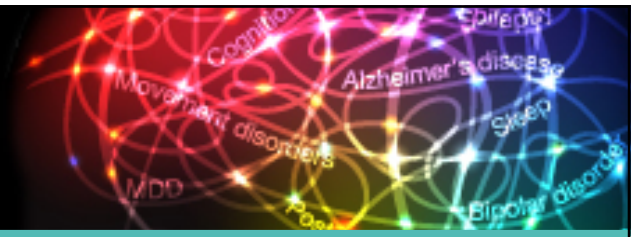
Montagne A, et al. *Acta Neurpathol*. 2016;131:687-707.
Images from emedicine.medscape.com and Wikimedia Commons website

# Use of Beta Amyloid PET Testing for Alzheimer's Disease (AD)

- Appropriate use:
  1) Progressive, unexplained mild cognitive impairment
  2) Possible AD, but atypical course
  3) Progressive dementia, but with atypical early onset
- Inappropriate use:
  1) Probable AD with typical age of onset
  2) Staging of severity of AD
  3) Prediction of future risk (i.e., APOE e4 +)

Johnson KA et al. *Alzheimers and Dement*. 2013;9 e1-e16.

# Current Treatments for AD Offer Modest Benefits




- All ChEIs (donepezil, rivastigmine, and galantamine) are approved for mild to moderate AD; donepezil and rivastigmine also is approved for moderate to severe AD in the US
- Memantine is approved for moderate to severe AD, either alone or in combination with ChEIs,[1] and for mild AD in some countries (eg, Russia, Mexico)
- Until recently, the maximum approved doses were donepezil 10 mg/day, rivastigmine 9.5 mg/24h and memantine 20 mg/day[1]
- These dosages are associated with modest beneficial effects in managing cognitive deterioration in patients with moderate to severe dementia[2,3]

ChEI = cholinesterase inhibitor.

1. Singh I, Grossberg GT. *Curr Psychiatry*. 2012;11(6):20-29; 2. Raina P, et al. *Ann Intern Med*. 2008;148 (5):379-393; 3. Cummings J. *New Engl J Med*. 2004;351(1):56-67.

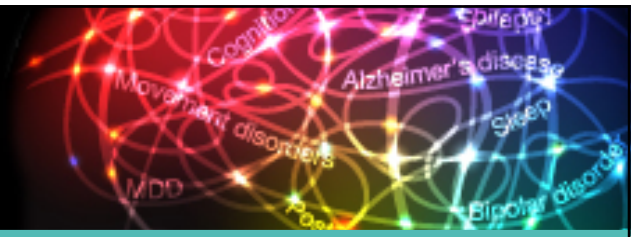
# FDA-Approved Treatments for AD Cognitive Decline

| Drug | Maximum daily dose | Mechanism of action | Indication | Common side effects/comments |
|---|---|---|---|---|
| Tacrine | 160 mg/day | ChEI | Mild to moderate AD | Nausea, vomiting, loss of appetite, diarrhoea. First ChEI to be approved, but rarely used because of associated possible hepatotoxicity |
| Donepezil | 10 mg/day | ChEI | All stages of AD | Nausea, vomiting, loss of appetite, diarrhoea, sleep disturbance |
| Rivastigmine | 12 mg/day | ChEI | All stages of AD | Nausea, vomiting, diarrhoea, weight loss, loss of appetite |
| Galantamine | 24 mg/day | ChEI | Mild to moderate AD | Nausea, vomiting, diarrhoea, weight loss, loss of appetite |
| Memantine | 20 mg/day | NMDA receptor antagonist | Moderate to severe AD | Dizziness, headache, constipation, confusion |
| Galantamine ER | 24 mg/day | ChEI | Mild to moderate AD | Nausea, vomiting, diarrhoea, weight loss, loss of appetite |
| Rivastigmine transdermal system | 13.3 mg/day | ChEI | Mild to moderate AD | Nausea, vomiting, diarrhoea, weight loss, loss of appetite |
| Donepezil 23 | 23 mg/day | ChEI | Moderate to severe AD | Nausea, vomiting, diarrhoea |
| Memantine XR | 28 mg/day | NMDA receptor antagonist | Moderate to severe AD | Dizziness, headache, constipation, confusion |

ER/XR = extended release, NMDA = N-methyl-D-aspartate.

Singh I, Grossberg GT. *Curr Psychiatry* 2012;11(6):20-29.

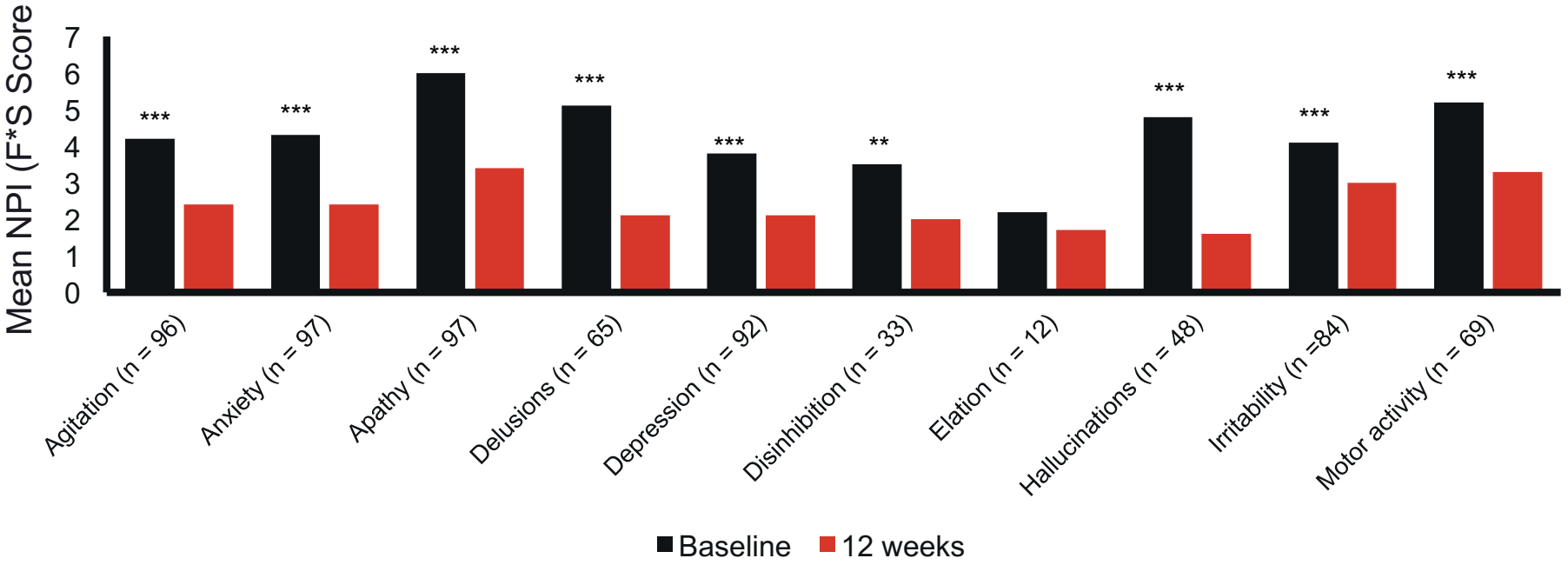
# Combination Therapy for Alzheimer's Disease




- Review of combination studies in mild-to-moderate and moderate-to-severe AD demonstrated:
  - Combination therapy (CT) with cholinesterase inhibiters (donepezil, galantamine, rivastigmine) plus memantine showed better outcomes than for placebo add-on with respect to measures of cognition, daily function, behavior and global outcome
  - The strongest evidence supporting the superiority of CT over ChEI monotherapy derives from a 24-week pivotal phase III clinical trial of addition of memantine to chronically stable donepezil treatment in highly selected subjects with moderate-to-severe AD

Patel L, Grossberg GT. *Drugs Aging*. 2011;28(7):539-546.

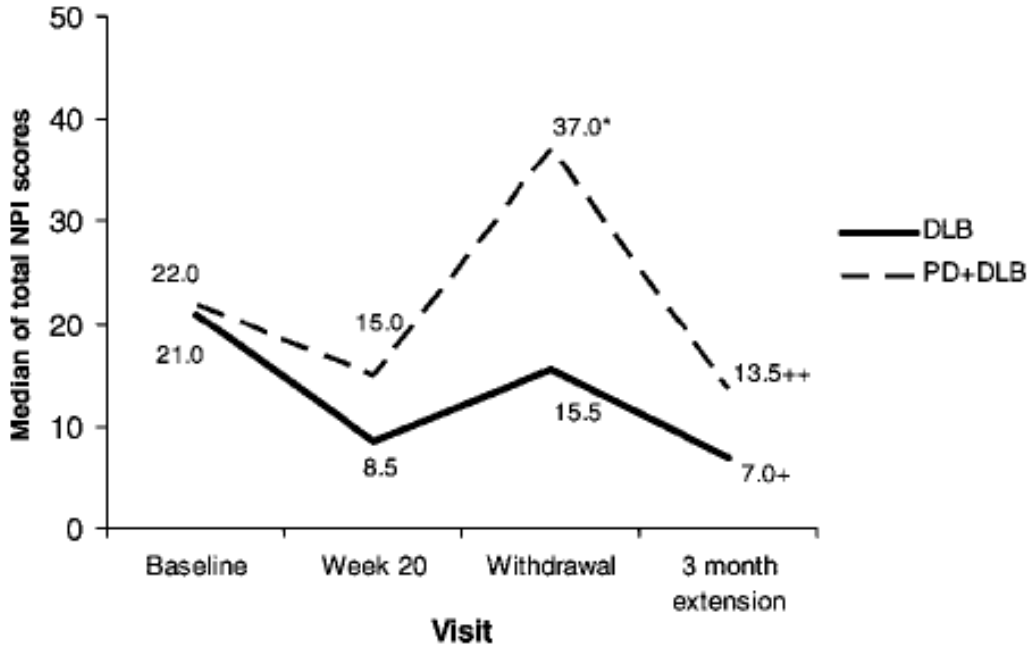
# Changes in NPI Item Scores With Donepezil




***$p < .0001$, **$p < .005$.
NPI = neuropsychiatric inventory
Holmes C, et al. *Neurology*. 2004;63:214-219.

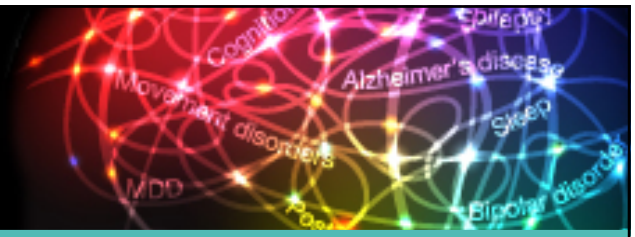
# Impact of Donepezil Withdrawal on NPI in Patients With Lewy Body Dementia and Parkinson Disease Dementia

- Of the 19 patients enrolled: 10 patients (4 patients with DLB, 6 patients with PD) were asked to restart treatment before completion of the 6 week withdrawal period due to marked clinical deterioration




Minnett TS, et al. *Int J Geriatr Psychiatry*. 2003;18:988-993.

# NCD-related Agitation

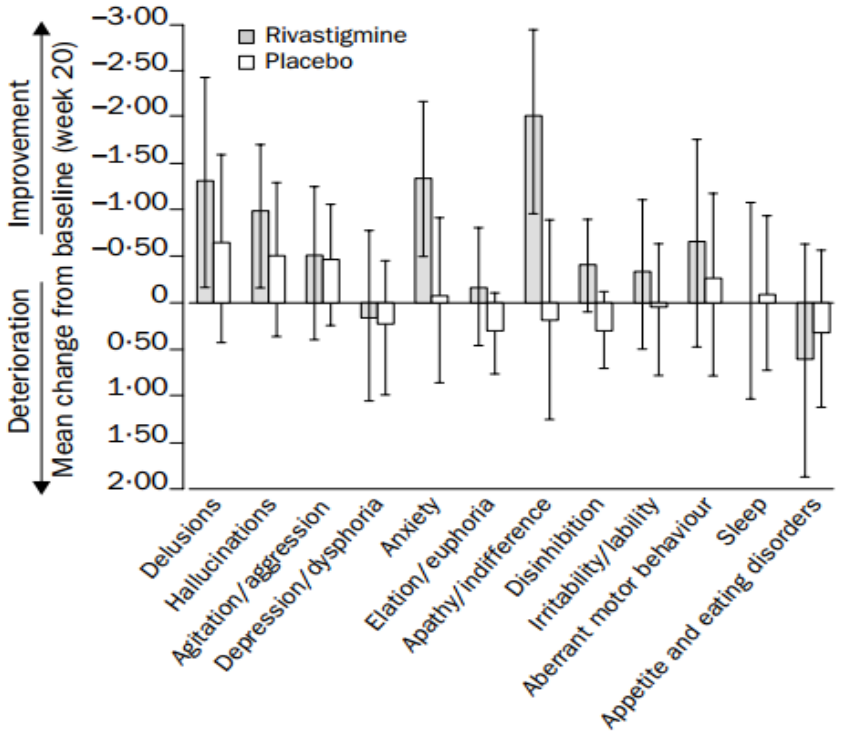



- If the change in mental status is acute, consider acute medical cause as a source of distress, leading to distressed behavior
  - UTI
  - Bad tooth
  - Constipation

# Cholinesterase Inhibitors and NMDA Receptor Antagonists: Effects on NCD-related Agitation

Anticholinesterase inhibitors:

- Donepezil (10 mg/day) with no benefits for agitation in a 12-wk placebo controlled study.[1]
- Rivastigmine (12mg/day) was superior to placebo in patient with Lewy body NCD[2]
- Memantine:
  - A 12 wk double-blind RCT of participants with AD and clinically significant agitation (N = 153) showed no benefits compared to placebo.[3]



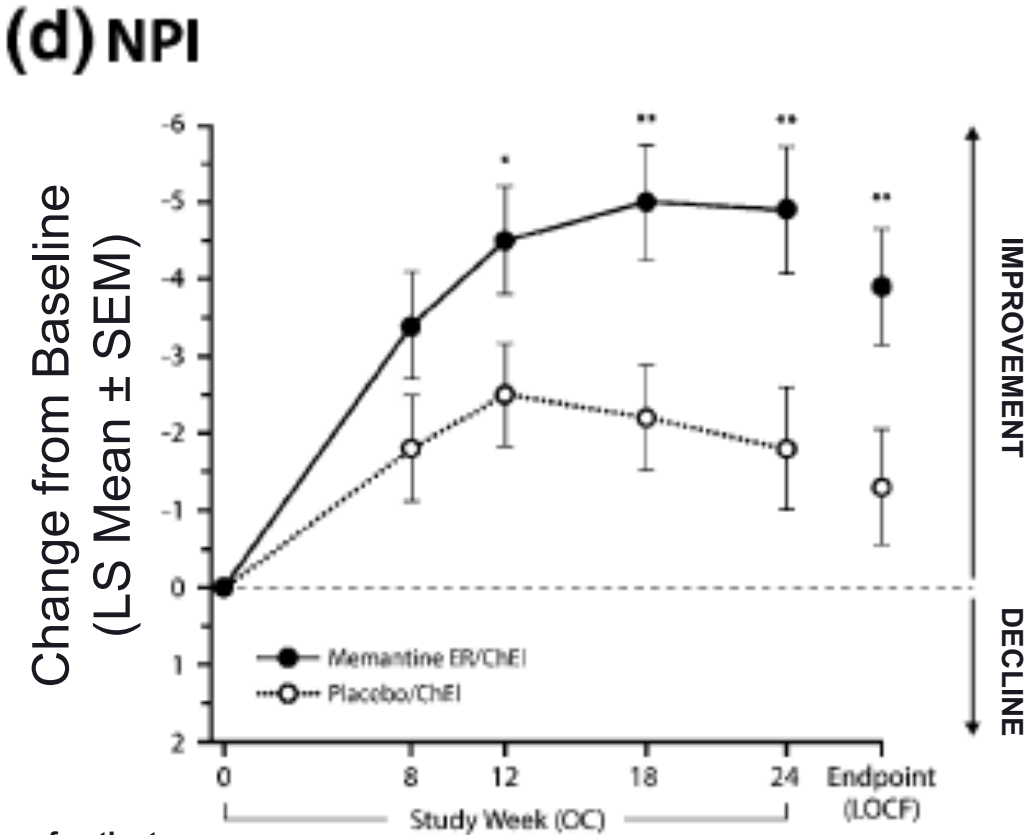

Howard RJ, et al. *New Engl J Med*. 2007;357:1382-1392.; McKeith I, et al. *Lancet*. 2000;356(9247):2031-2036.; Fox C, et al. *PLoS One*. 2012;7(5):e35185.

# Changes in NPI Item Scores With Memantine Compared With Donepezil

| | Memantine (Mean ± SD) | Donepezil (Mean ± SD) | *P* value |
|---|---|---|---|
| Delusions | -0.55±1.546 | -0.40±1.808 | 0.594 |
| Hallucinations | -0.40±1.382 | -0.19±0.730 | 0.246 |
| Agitation* | -0.49±1.684 | -0.04±0.829 | 0.039 |
| Depression | -0.38±1.126 | -0.15±0.817 | 0.144 |
| Anxiety | -0.42±1.433 | -0.16±0.871 | 0.175 |
| Euphoria | -0.08±0.493 | -0.21±1.277 | 0.413 |
| Apathy | -0.89±2.125 | -0.96±2.391 | 0.852 |
| Disinhibition | -0.12±0.551 | -0.17±0.828 | 0.667 |
| Irritability | -0.89±1.696 | -0.64±1.539 | 0.348 |
| Aberrant motor behavior | -0.14±1.326 | -0.16±1.079 | 0.908 |
| Nighttime behavior disturbances | -1.07±2.244 | -0.65±1.672 | 0.203 |
| Appetite and eating abnormalities | -0.18±1.262 | 0.13±0.935 | 0.090 |

SD = standard deviation.*Significant differences in agitation between memantine and donepezil.;
Zhang N, et al. *Dement Geriatr Cogn Disord*. 2015;40:85-93.

# Impact of Memantine on NPI Scores




| Number of patients | | | | | | |
|---|---|---|---|---|---|---|
| Memantine ER/ChEI: | 333 | 304 | 288 | 276 | 268 | 318 |
| Placebo/ChEI: | 328 | 307 | 302 | 289 | 272 | 321 |
| Between-group difference (*p* values) | | 0.062 | **0.019** | **0.001** | **0.002** | **0.005** |

*$p < .05$, †$p < .01$.

Grossberg GT, et al. *CNS Drugs*. 2013;27:469-478.

# Antipsychotics for NCD-related Agitation


- Atypical antipsychotics demonstrate at best modest benefit for neuropsychiatric symptoms in dementia[1]
- In the CATIE trial, improvement was observed in 32% of patients assigned to olanzapine, 26% of patients assigned to quetiapine, 29% of patients assigned to risperidone, and 21% of patients assigned to placebo
  - However, results were not statistically significantly different from placebo ($p = 0.22$).[2]
  - Analyses indicated that individual symptoms, such as anger, aggression, and paranoid ideas were more likely to improve with antipsychotics[3]

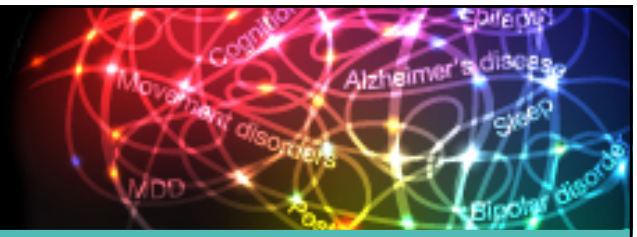
1. Steinberg M, et al. *Am J Psychiatry*. 2012;169(9):900-906.; 2. Schneider LS, et al. *New Engl J Med*. 2006;355:1525-1538.; 3. Sultzer DL, et al. *New Engl J Med*. 2008;165(7):844-854

# Antipsychotics for NCD-related Agitation


- Black box warning: Meta-analysis of 17 RCTs with 1.6-1.7 fold increase in mortality in elderly patients with NCD associated with olanzapine, aripiprazole, risperidone and quetiapine.[1]
  - Two studies found typical antipsychotics have higher mortality compared to atypicals.[2]
- Quetiapine appears to be safest[3]

1. FDA. https://www.fda.gov/Drugs/DrugSafety/ucm053171.htm
2. FDA. https://www.fda.gov/Drugs/DrugSafety/ucm124830.htm.
3. Kales HC, et al. *Am J Psychiatry*. 2012;169(1):71-79.

# Medications for NCD-related Agitation




- Avoid language that inadvertently gives the appearance that medications are being used as chemical restraint
- Document using patient-focused language
- If antipsychotics are prescribed, then try to document some psychosis
- If antipsychotics are prescribed, discuss risks with caregivers and loved ones and document

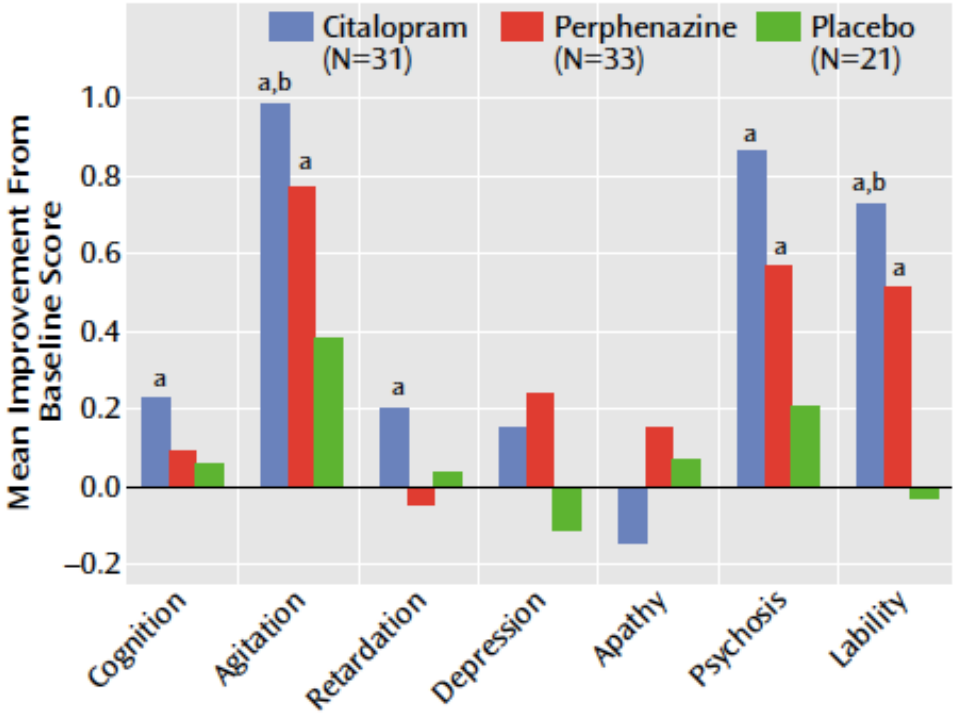
# SSRIs for NCD-related Agitation and Depression


- Depression in Alzheimer Disease Study (DIADS)[1]
  - Sertraline (25-150 mg/day) group had greater improvement in the depression scores (9 vs 3 full responders and 11 vs 4 partial responders) in double-blind placebo-controlled trial (N = 44)
  - In full responders and partial responders – activities of daily living, behavioral disturbance and caregiver distress also improved.
- Citalopram for Agitation in Alzheimer Disease (CitAD)[2]
  - Citalopram (30 mg/day) reduced Alzheimer disease related agitation and caregiver distress in double-blind placebo-controlled trial (N = 186).
  - No improvement in activities of daily living
  - Citalopram group had worsening cognition scores and prolongation of QT interval

1. Lyketsos CG, et al. *Arch Gen Psychiatry*. 2003;60(7):737-746.
2. Porsteinsson AP, et al. *JAMA. 2014*;311(7):682-691.

# Efficacy of Citalopram on Agitation in AD

- Change in neurobehavioral factor scores from baseline to study termination (≤ 17 days) in patients with dementia in a randomized, double-blind, placebo-controlled trial of citalopram and perphenazine




[a]Significant difference within group between baseline and termination scores ($p < .05$).; [b]Significant difference between the citalopram and placebo groups ($p < .05$).; BG, et al. *Am J Psychiatry*. 2002;159:460-465.

# Mood Stabilizers for NCD-related Agitation


**Valproate:**

- 24-month placebo controlled trial (N = 122) showed no delay in onset of agitation of psychosis in moderate AD[1]
- Associated with significant toxic effects[1] and comparable to antipsychotics[2]

**Carbamazepine**:

- Short-term improvement in CGI compared to placebo[3,4]

**Lithium:**

- Ongoing Phase II trial (clinicaltrials.gov)

CGI = clinical global impression.

1. Tariot PN, et al. *Arch Gen Psychiatry*. 2011;68(8):853-861; 2. Kales HC, et al. *Am J Psychiatry*. 2012;169(1):71-79; 3. Tariot PN, et al. *Am J Psychiatry*. 1998;155(1):54-61.4. Olin JT, et al. *Am J Geriatr Psychiatry*. 2001;9(4):400-405.

# Antihypertensives for NCD-related Agitation


**Propranolol:**

- Adjunctive propranolol (mean dose of 106 mg/day) was superior to placebo for treating agitation in AD (N = 31).
- Efficacy was lost after 6 months.[1]

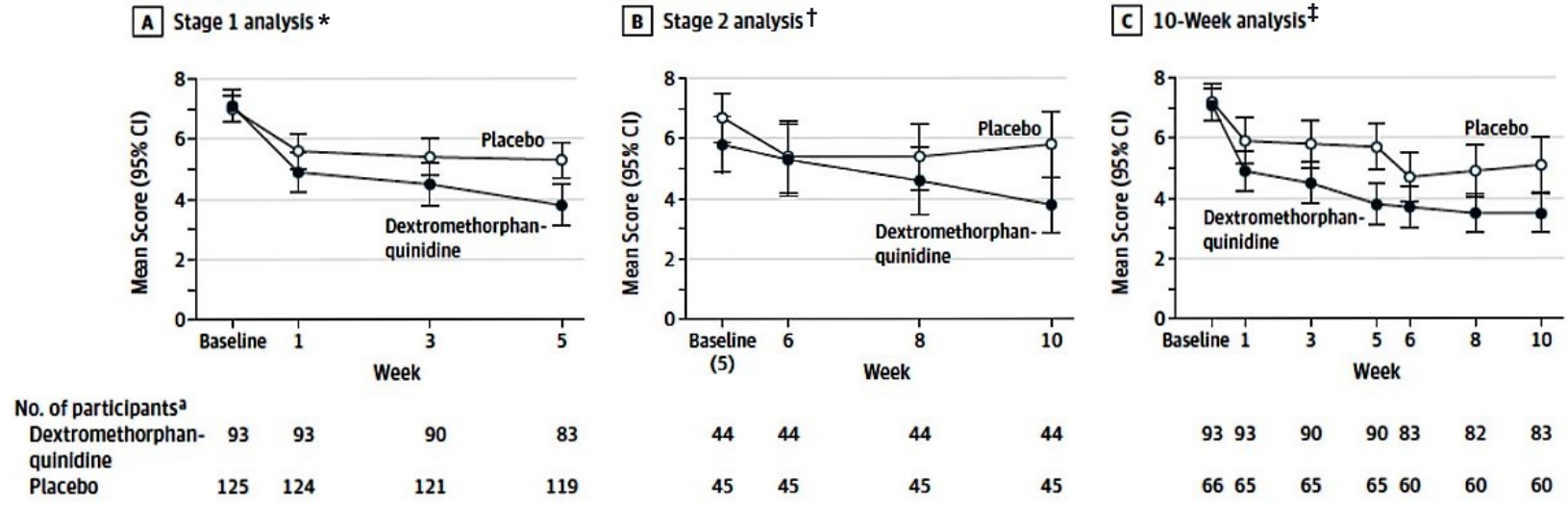
**Prazosin:**

- Prazosin (mean dose 6mg/day) improved agitation/aggression in AD in a double-blind placebo-controlled study (N = 22).
- Prazosin was well tolerated.[2]

1. Peskind ER, et al. *Alzheimer Dis Assoc Disord*. 2005;19(1):23-28
2. Wang LY, et al. *Am J Geriatr Psychiatry*. 2009;17(9):744-751.

# Dextromethorphan-Quinidine for NCD-related Agitation (FDA-Approved for Pseudobulbar Affect)

- Randomized, multicenter, double-blind placebo-controlled trial (N =194) showed efficacy in AD agitation
- NMDA receptor antagonist, 5HT and NE reuptake inhibition, and nicotinic α3β4 receptor antagonism.
- Effects on NPI Agitation subscale (scored 0-12)
- Treatment-emergent adverse events – Falls, diarrhea, UTI, dizziness




*Stage 1 analysis = Wks 1-5, Stage 2 Analysis = †Wks 6-10 for placebo nonresponders randomized after stage 1, ‡10 week analysis = only patients who continued the same treatment assignment throughout the study, observed cases.; NE = norepinephrine, 5-HT = 5-hydroxytryptamine.

Cummings JL, et al. *JAMA*. 2015;314(12):1242-1254.

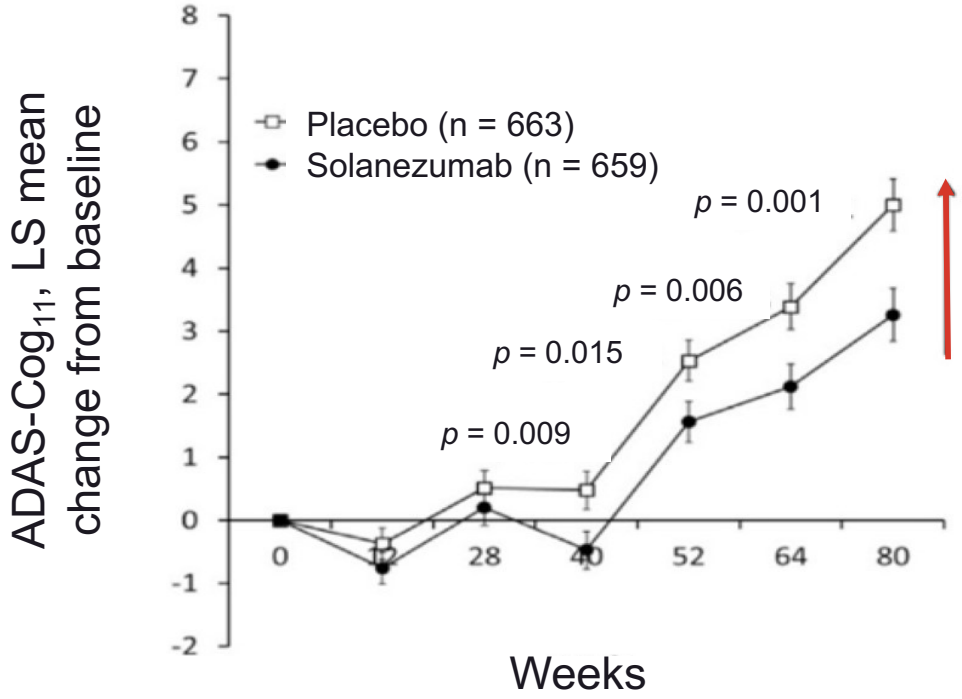
# Classes of Agents in Phase 3


| Antiamyloid Disease-Modifying | Neuroprotective /Metabolic | Cognitive Enhancing | Neuropsychiatric |
|---|---|---|---|
| •Amyloid immunotherapies<br>•BACE inhibitors<br>•RAGE inhibitor<br>•Calcium channel blocker | •Insulin<br>•PPAR-γ agonist (pioglitazone)<br>•Anti-inflammatory<br>•AC-104 (ketones)<br>•Anti-tau agents | •5-$HT_6$ antagonist (idalopirdine; RVT-101)<br>•Cannabinoid antagonists | •AVP-786 (DM/Q)<br>•Brexpiprazole<br>•Aripiprazole |

BACE = beta-site amyloid precursor protein cleaving enzyme, RAGE = receptor for advanced glycation endproducts, PPAR = peroxisome proliferator-activated receptor.

# Combined EXPEDITION 1 and 2 Data for Solanezumab in Mild and Moderate AD

Pooled data from EXPEDITION 1 and 2 show less decline from baseline in ADAS-Cog scores



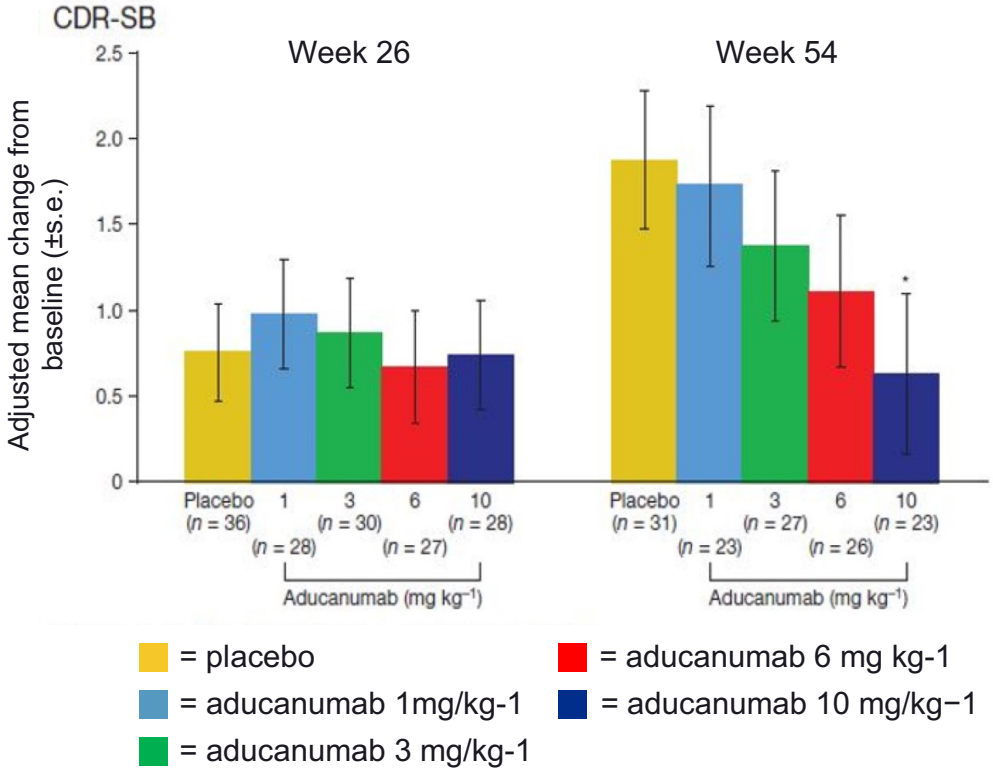

Modeled mean group difference (95% CI): 1.141 (0.35, 2.47)
*p* = .009

ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognition.

Siemers E, et al. *Alzheimer's Dement*. 2016;12:110-120.

# PRIME CDB-SB Data for Aducanumab

- Change from baseline on the CDR-SB
  - Demonstrated dose-dependent slowing of clinical progression with aducanumab treatment at one year
  - Dose-response, $p < .05$, with the greatest slowing for 10 mg $kg^{-1}$ ($p < .05$ versus placebo)




CDR-SB = clinical dementia rating scale-sum of boxes.

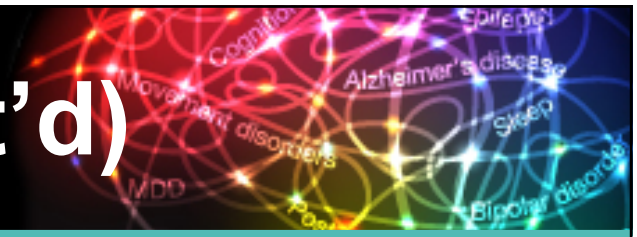
Sevigny J, et al. *Nature*. 2016;537:50-56.

# Clinical Connections


- Diagnosis of neurocognitive disorders can be guided by new diagnostic language in *DSM-5* and when appropriate, by imaging or biomarkers
- Major and mild neurocognitive disorders exist on a spectrum of cognitive and functional impairment. Major neurocognitive disorders corresponds to the condition referred to in *DSM-IV* as dementia
- Neuropsychological testing, with performance compared with norms appropriate to the patient's age, educational attainment, and cultural background, ideally is part of the standard evaluation of neurocognitive disorders and is particularly critical in the evaluation of mild neurocognitive disorders
- If neuropsychological testing is unavailable, a variety of brief office-based or "bedside" assessments are available (ex, GPCOG, Mini-Cog™, MIS)

GPCOG = general practitioner assessment of cognition, MIS = memory impairment screen.

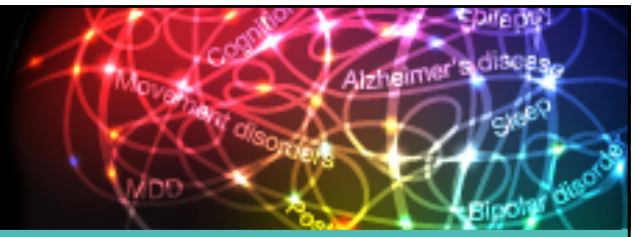
# Clinical Connections (Cont'd)




- There are few FDA-approved treatments for cognitive deficits in AD
- We now have some non-FDA approved options for the treatment of agitation in AD
- Several agents are being evaluated in clinical trials

Singh I, Grossberg GT. *Curr Psychiatry* 2012;11(6):20–29; Farlow MR, et al. *Clin Ther* 2010; 32 (7): 1234–1251; Cummings J, et al. *Dement Geriatr Cogn Disord*. 2012;33(5):341-353; Atri A, et al. *Alzheimer Dis Assoc Disord.* 2008; 22(3):209-221.

# Call to Action



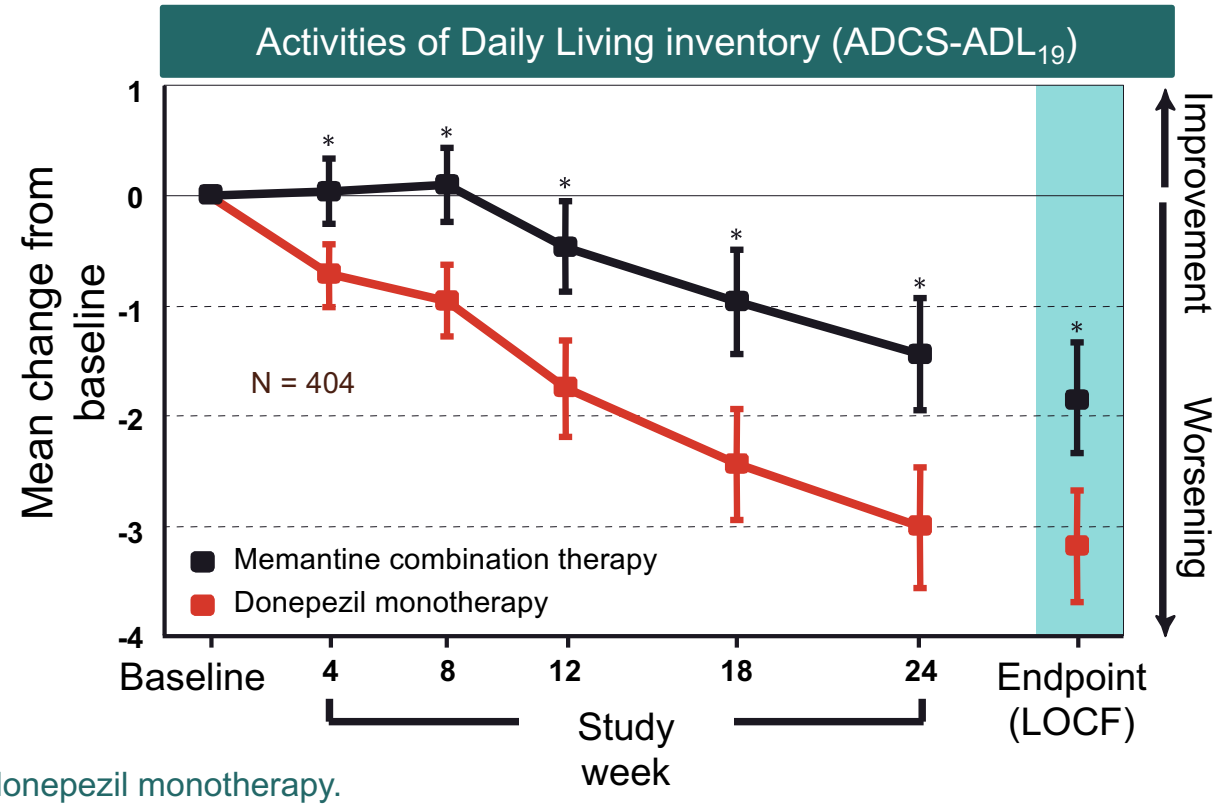

- Integrate neuropsychological testing into the standard evaluation of neurocognitive disorders and in the evaluation of mild neurocognitive disorders
- When prescribing antipsychotics for patients with AD and behavioral disturbances, discuss the risks with caregivers and loved ones, and document the conversation

# Questions & Answers

Don’t forget to fill out your evaluations to collect your credit.

# Resource Slides

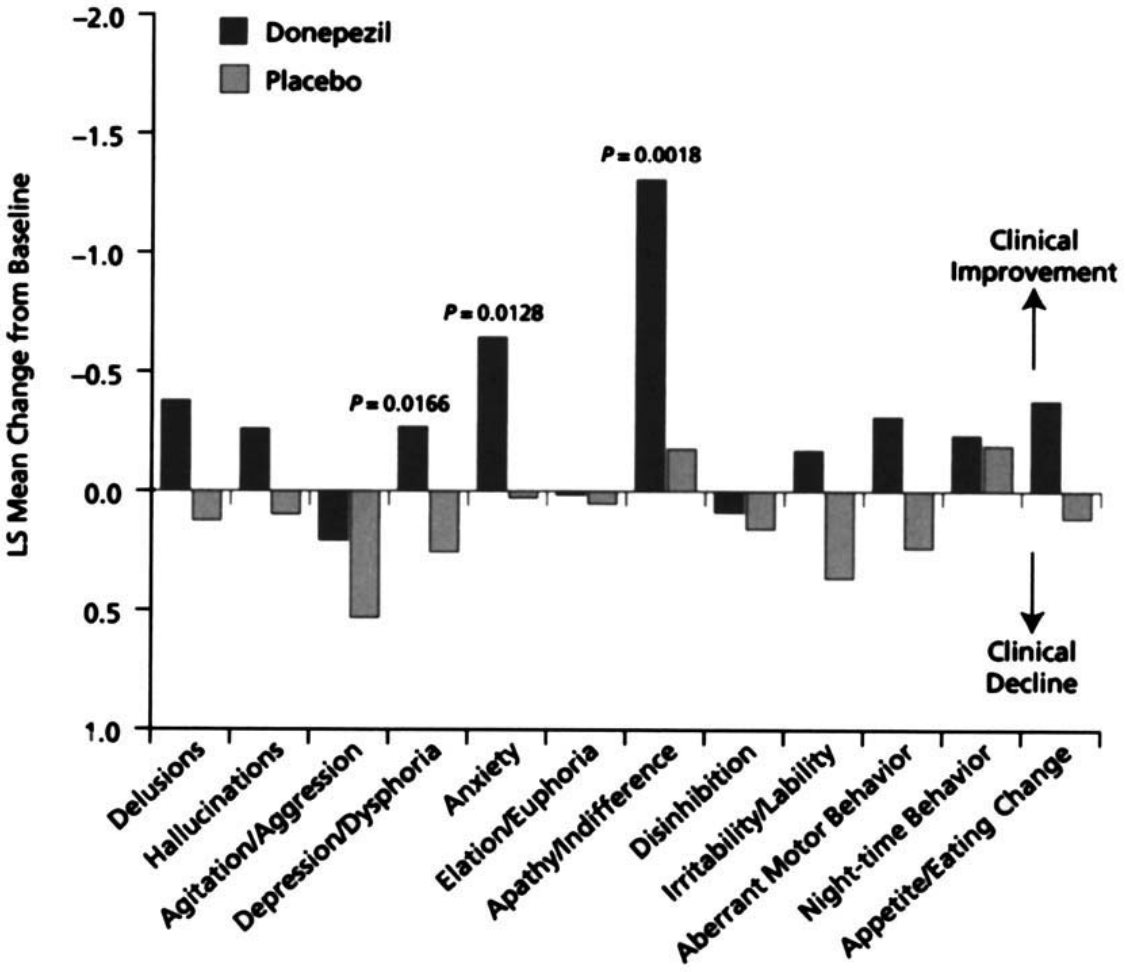
# Donepezil With and Without Memantine: Effects on Function




*$P < .05$ vs. donepezil monotherapy.

Tariot PN, et al. *JAMA*. 2004;291(3):317-324.

# Efficacy of Donepezil on Behavior in AD




Gauthier S, et al. *International Psychogeriatrics*. 2002;14:4:389-404.