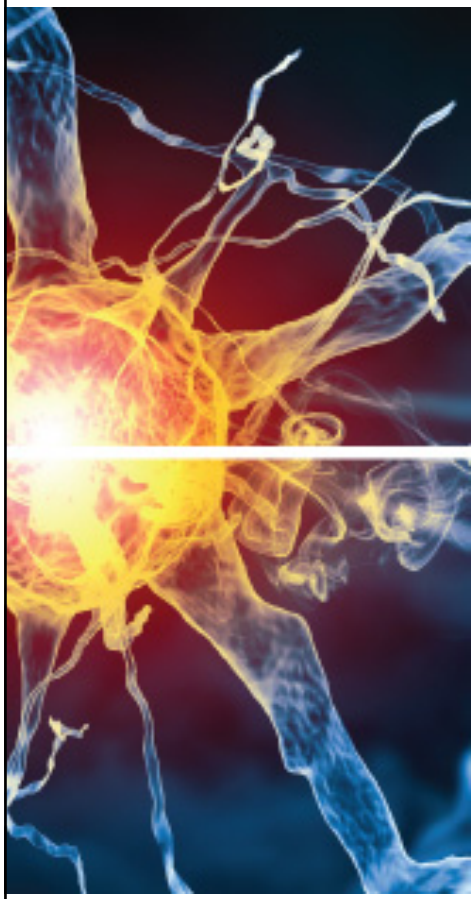
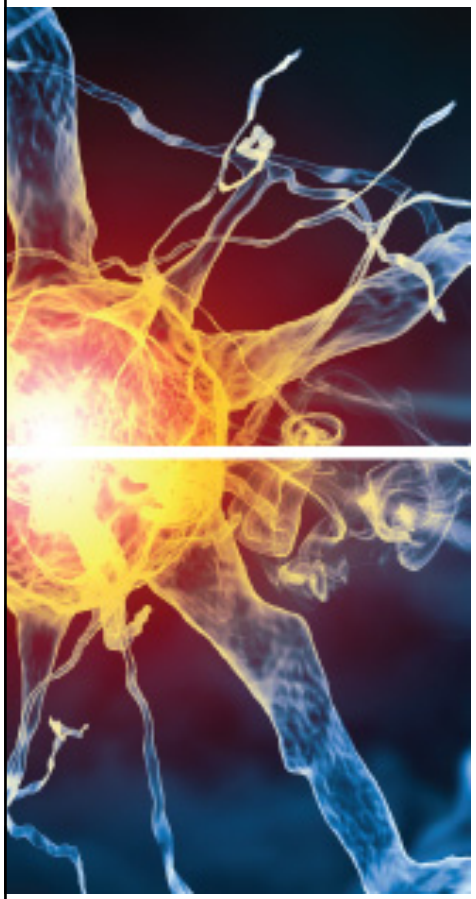


Neurocognitive Disorders

Research to Emerging Therapies



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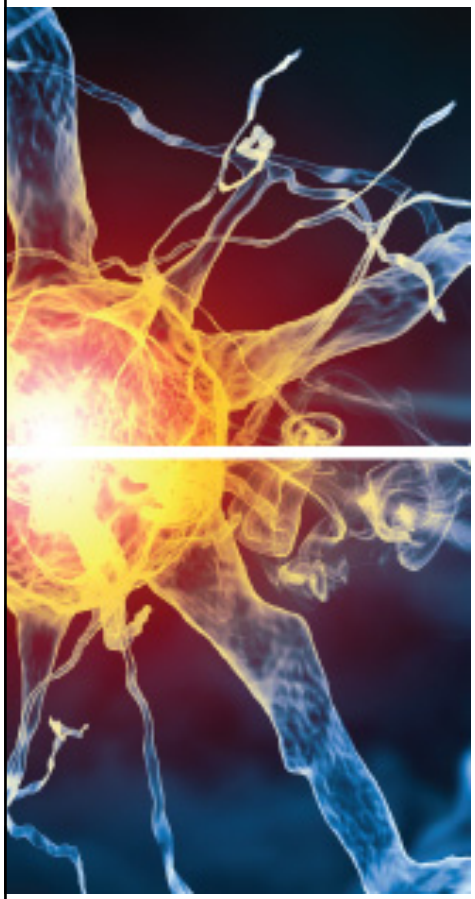
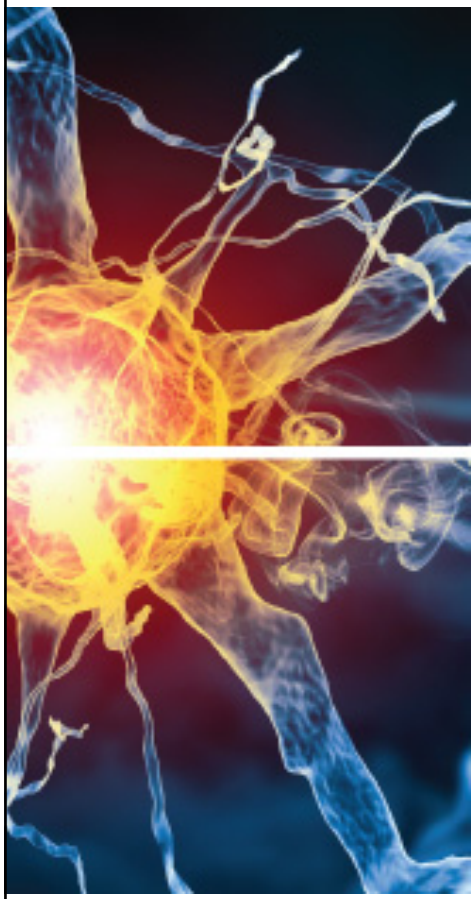
Disclosures

- Dr. Huey has no disclosures to report.



1 Learning Objective

Review the current treatments for neurodegenerative disorders.

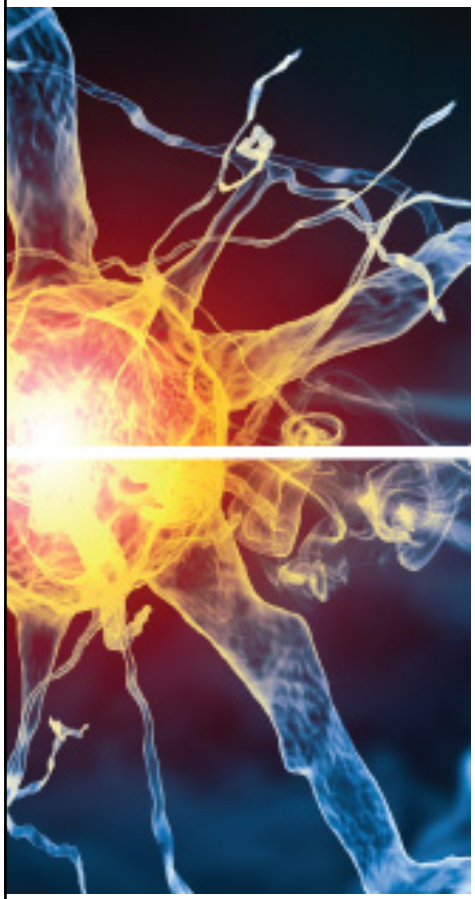


2 Learning Objective

Describe future strategies for the the management of neurodegenerative disorders.

Outline

- Current treatments for neurodegenerative disorders
  - Memory symptoms
  - Neuropsychiatric symptoms
    - Agitation
    - Depression
- Future directions
  - Earlier treatment
  - Pathology-based treatments across clinical diagnoses
  - Treatments based on genetic findings



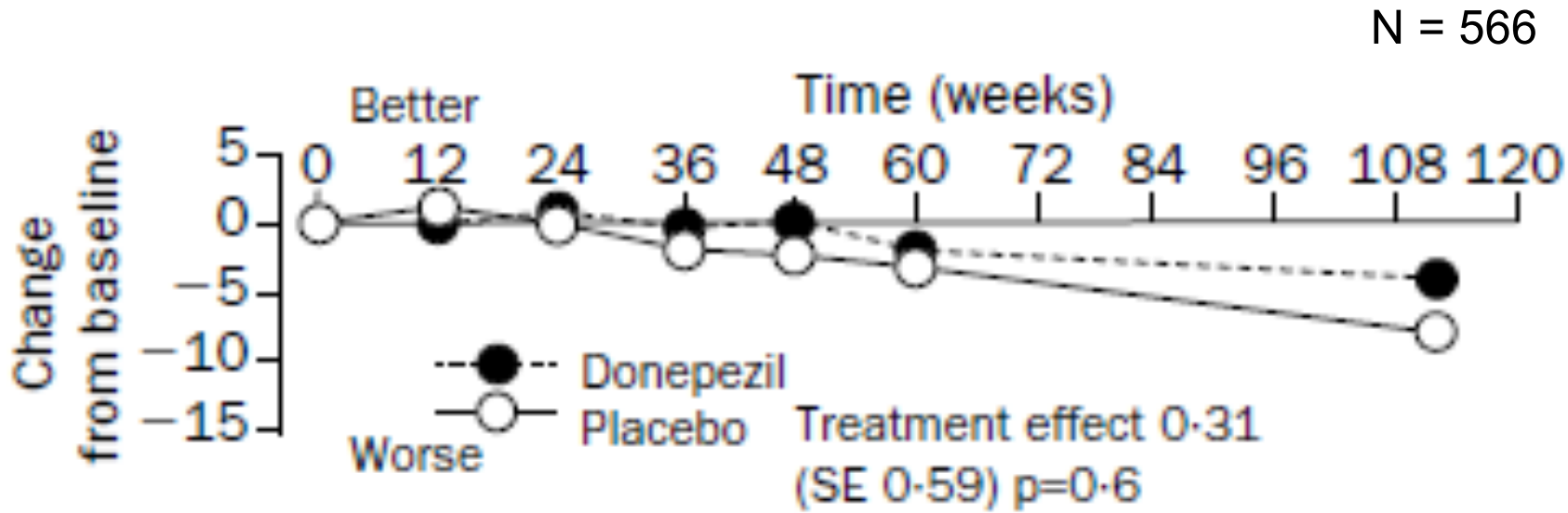
Existing Treatments for Memory Symptoms in Alzheimer's Disease (AD)

Treatment for Memory Symptoms in AD

- Cholinesterase inhibitors
  - Donepezil
  - Rivastigmine
  - Galantamine
  - Memantine, a NMDA antagonist

NMDA = N-methyl-D-aspartate.

Cholinesterase Inhibitors: Efficacy



Courtney C, et al. *Lancet*. 2004;363(9427):2105-2115.

Cholinesterase Inhibitors: Efficacy

- In a pooled meta-analysis[1] (N = 7954), 9% of patients treated "responded"
  - NNT for one patient to receive benefit is:
    - 7 for stabilization or better
    - 12 for minimal improvement or better
    - 42 for marked improvement
  - NNH is 12
- In a meta-analysis[2] treated patients:
  - ↑0.1 SD on ADL scales and 0.09 SD IADL scales compared with placebo, an effect that would be similar to preventing a two month per year decline in a typical patient with AD

NNT = number needed to treat; NNH = number needed to harm, ADL = activities of daily living, SD = standard deviation, IADL = instrumental activities daily living.

[1]Lanctôt KL, et al. *CMAJ*. 2003;169(6):557-564; [2]Geldmacher DS. *Expert Rev Neurother.* 2004;4(1):5-16.

Cholinesterase Inhibitors: Adverse Events and Interactions

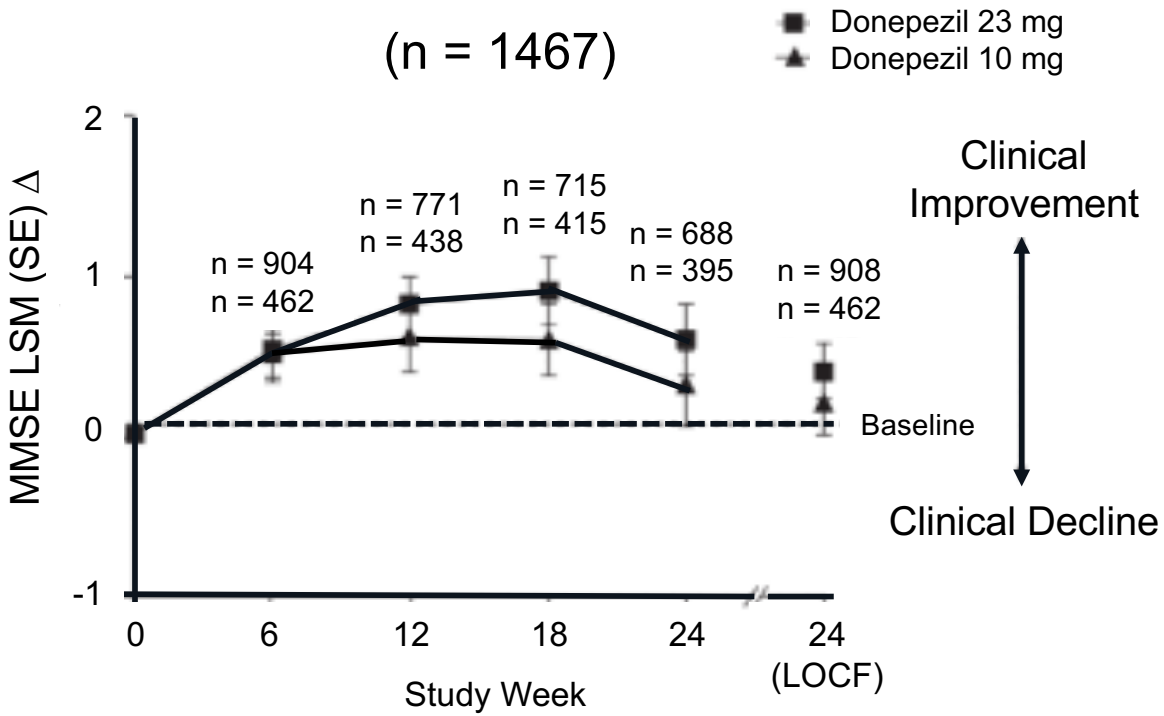
- Nausea or decreased appetite (3-19%)
- Insomnia (2-14%)
- Depression (2-3%)
- Intense dreams (2-3%)
- Minor CYP2D6 CYP3A4 substrate

Donepezil [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208328orig1s000lbl.pdf

Rivastigmine [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/022083lbl.pdf

Galantamine [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/021615lbl.pdf

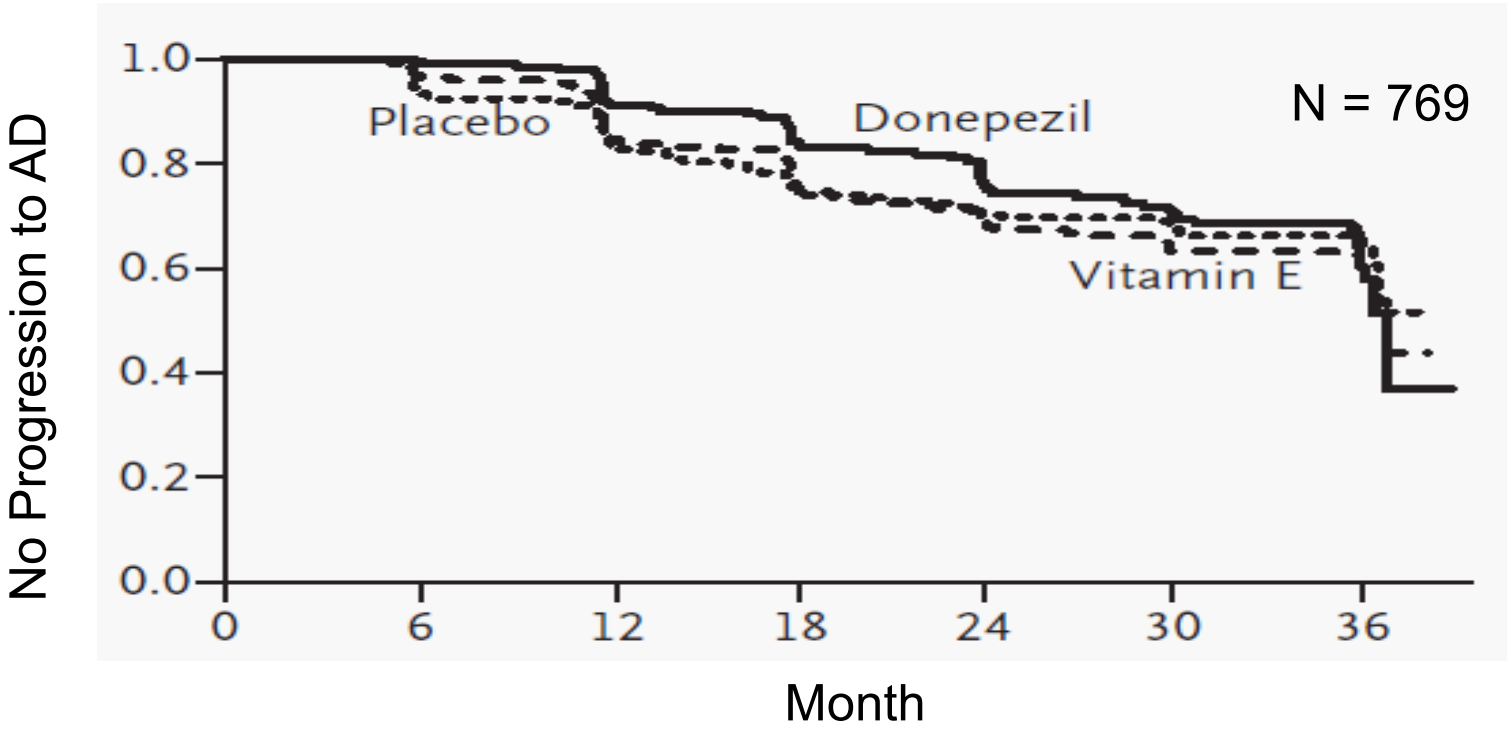
Donepezil: 10 mg vs 23 mg



MMSE = Mini Mental State Examination

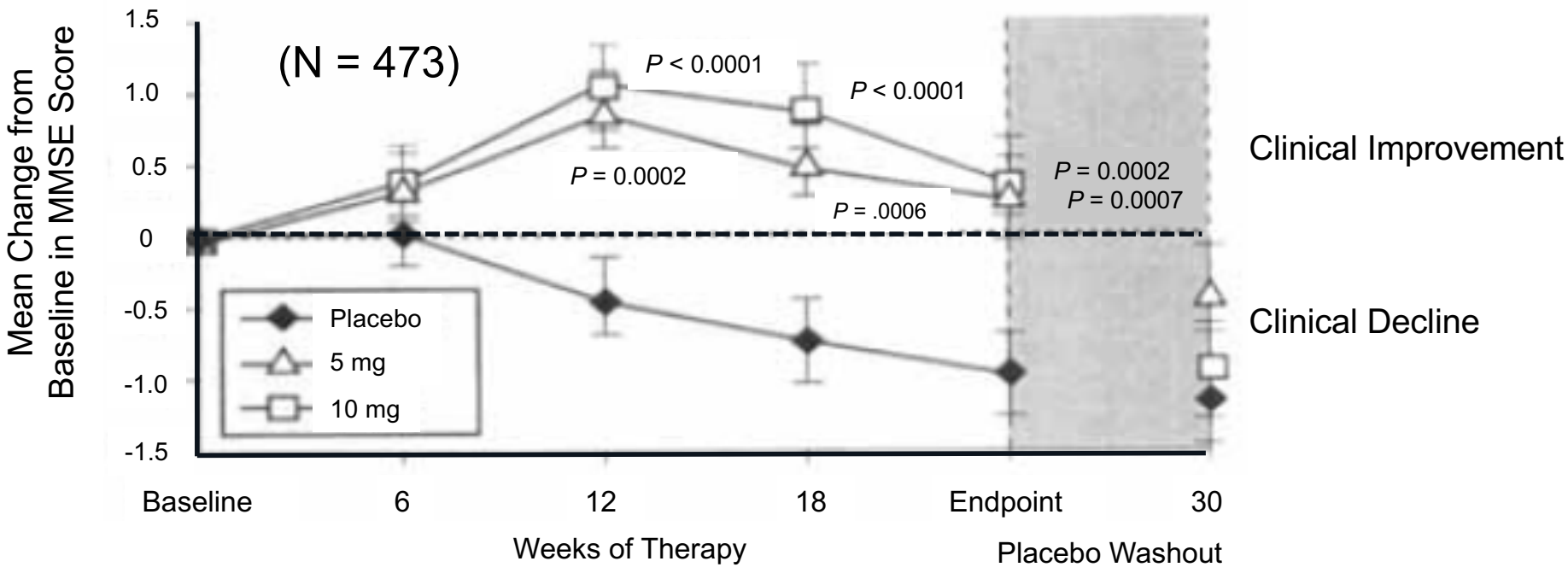
Farlow MR, et al. *Clin Ther.* 2010;32(7):1234-1251.

Cholinesterase Inhibitors* and MCI



*Not FDA approved for MCI.
MCI = mild cognitive impairment.
Petersen RC, et al. *N Engl J Med.* 2005;352(23):2379-2388.

Discontinuing Cholinesterase Inhibitors



Rogers SL, et al. *Neurology*. 1998;50(1):136-145.

Cholinesterase Inhibitors* in Other Types of Dementia

- Demonstrated efficacy in:
  - Lewy body dementia
  - Vascular dementia
  - Parkinson's disease dementia
- Has not demonstrated efficacy in other cognitive disorders

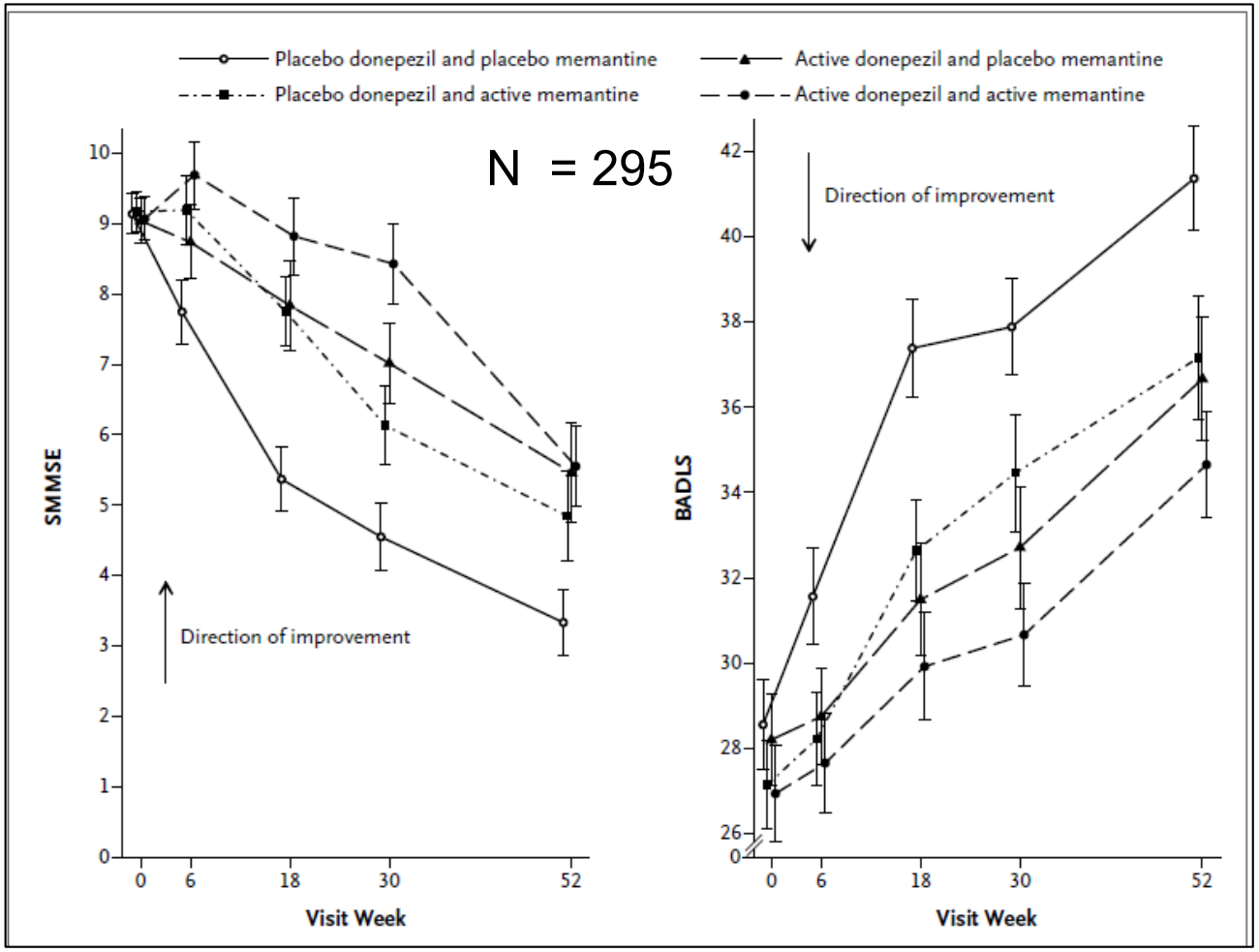
*Not FDA approved for Lewy body dementia, vascular dementia or Parkinson's disease dementia.

Aarsland D. *Parkinsonism Relat Disord*. 2016;22 Suppl 1:S144-S148; Amenta F, et al. *Clin Exp Hypertens*. 2002;24(7-8):697-713.

Memantine

Mean Scores on the Standardized Mini-Mental State Examination (SMMSE)

- Scores on the SMMSE range from 0 to 30 with higher scored indicating better cognitive function
- Scores on the BADLS range from 0 to 60 with higher scores indicating greater impairment
- Shown are raw estimates of the mean score at each visit



Howard R, et al. *New Engl J Med*. 2012;366(10):893-903.

An Algorithm for the Treatment of Memory Symptoms in AD

- Start oral cholinesterase inhibitor
- If GI adverse effects, change to rivastigmine patch
- Adverse effects to donepezil and rivastigmine patch, consider not treating with cholinesterase inhibitor
- Once stable on cholinesterase inhibitor, consider adding memantine
- Continue cholinesterase inhibitor and memantine unless reason to stop (e.g., weight loss)

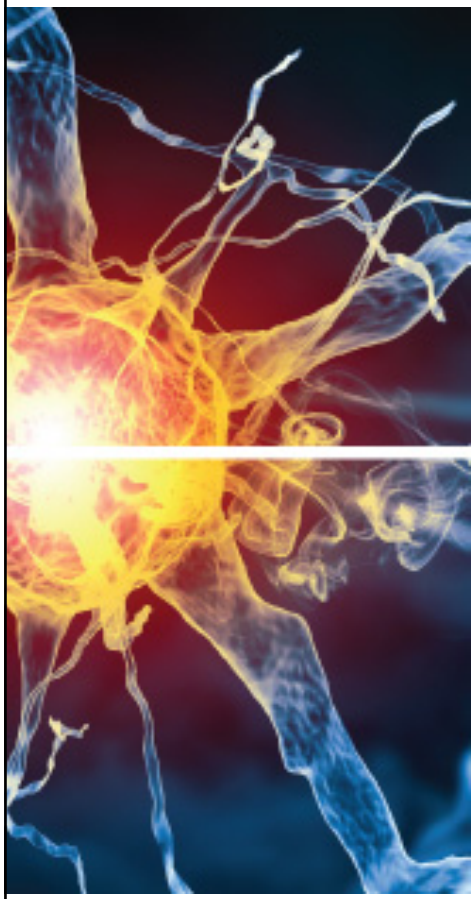
GI = gastrointestinal.

Cummings JL, et al. Ann Clin Trans Neurol. 2015;2(3):307-323.

An Algorithm for the Treatment of Memory Symptoms in MCI

- Monitor patients with MCI
- If they show worsening, consider starting a cholinesterase inhibitor,* even if still in MCI range
- Take into account subtype of MCI:
  - Relatively low risk of progression to AD:
    - Dysexecutive MCI
  - Relatively high risk of progression to AD:
    - Multidomain MCI, including amnesia

*Not FDA approved for MCI.



Treating Neuropsychiatric Symptoms of Dementia

Agitation

- Agitation has a point prevalence of 11% in MCI and 30% in dementia
- Nonpharmacological treatment of agitation is very important
  - Setting
  - Home health aides
  - Behavior logs
  - Adjusting expectations
  - Physical interventions

Lyketsos et al. *JAMA*. 2002;288(12):1475-83.

Atypical Antipsychotics

- In AD, commonly used for behavioral symptoms
- In dementia, small effect size on behavioral symptoms (0.12 to 0.2)
- Increased OR of death of 1.54 (95% CI, 1.06-2.23; NNH = 87)
- Mostly comparable efficacy between meds
- Choose mostly based on side effects

OR = objective response; CI = confidence interval.

Maher AR et al. JAMA, 2011;306(12):1359-1369.

Atypical Antipsychotics, cont

- Risperidone*
  - Range: 0.5-2.5 mg
  - Can have more EPS than other atypicals at higher doses
- Quetiapine*
  - Range: 50-200 mg
  - Sedating, possibly less efficacious
- Olanzapine*
  - Range: 2-10 mg
  - Limited use in FTD because of appetite increase
- Aripiprazole*
  - Range: 2-15 mg

*Not FDA approved for AD.
EPS = extrapyramidal side effects.
[Package Inserts]. Drugs@FDA Website.

New Medications for Psychosis and Agitation in Dementia: Pimavanserin*

- Recently approved medication for psychosis associated with Parkinson's disease
- Mechanism is not fully understood, but inverse agonist and antagonist at serotonin 5-HT2A and 5-HT2C receptors
- Black box for increased mortality in elderly patients with Dementia-related psychosis.
- Can prolong QT interval
- Appears to be less likely to cause EPS than other antipsychotic medications

*Not FDA approved for AD. Pimavanserin [package insert]. Drugs@FDA.gov. 2016.

Dextromethorphan-Quinidine*

- A low-affinity, uncompetitive N-methyl-d-aspartate receptor antagonist, σ1 receptor agonist, serotonin and norepinephrine reuptake inhibitor, and neuronal nicotinic α3β4 receptor antagonist
- Has been used for years as a treatment for pseudobulbar affect
- Reduced agitation in AD patients
- Have to assess for possible medication interactions

*Not FDA approved for AD.

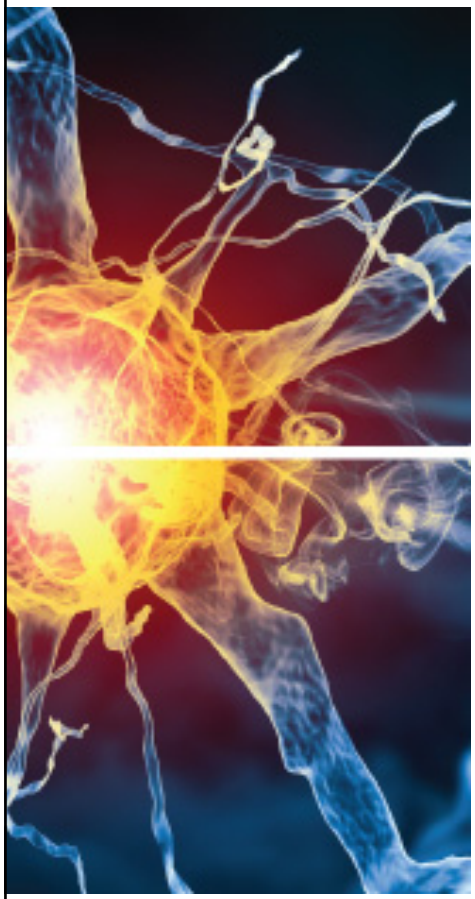
Cummings JL, et al. *JAMA*. 2015;314(12):1242-1254.
Dextromethorphan-quinidine [package insert]. Drugs@FDA.gov. 2010.

Other Medications for Agitation

- A review concluded that antidepressants were well tolerated, but “do not appear to be very effective for the treatment of neuropsychiatric symptoms in dementia except for depression”
- VPA* did not reduce agitation, but was associated with adverse effects
- Cholinesterase inhibitors were associated with a statistically significant, but questionably clinically significant, reduction of agitation

*Not FDA approved for AD. VPA, valproate.

Sink KM, et al. *JAMA.* 2005;293(5):596-608.

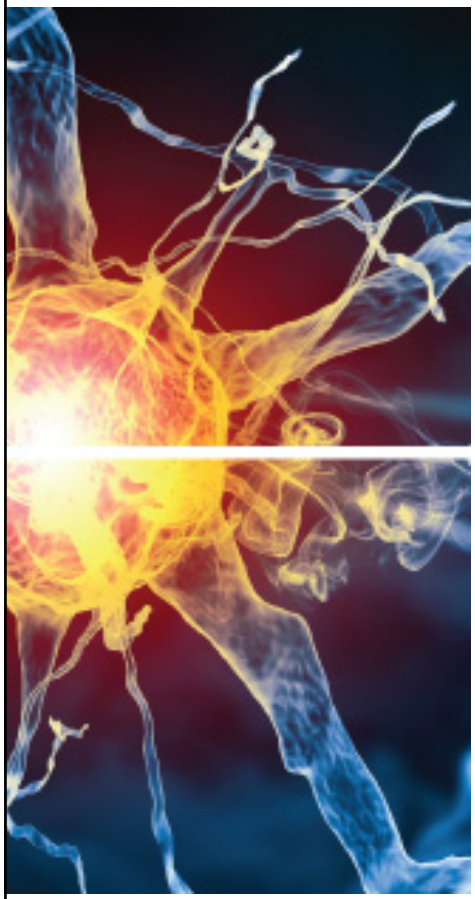


Depression

Depression and Dementia

- Depression on the NPI has a point prevalence of 20% in MCI and 32% in dementia
- Elderly patients who develop depression are at risk for developing AD
- Unlike antipsychotic medications, similar doses of antidepressants cab be used in older patients and younger patients with dementia
- Response rates lower than depression without AD

NPI, neuropsychiatric inventory.
Lyketsos CG, et al. *JAMA*. 2002;288(12):1475-1483.



Future Directions

Future Direction #1: Earlier Treatment

- **Example**: The “Anti-Amyloid Treatment in Asymptomatic Alzheimer’s study” (A4) study.
- Enrolling over 1,000 asymptomatic persons with elevated amyloid on amyloid-PET scan.
- Placebo vs active treatment with an antibody to amyloid: solanezumab*
- **Pros**: Could be successful where previous anti-amyloid therapies have not
- **Cons**: Previous anti-amyloid therapies have generally not been clinically successful

*Not FDA approved for AD.
https://clinicaltrials.gov/ct2/show/NCT02008357?term=a4+study+and+alzheimer&rank=1

Future Direction #2: Treatments Based on Pathology

- **Example**: BMS-986168* trial in progressive supranuclear palsy
- Trial of an anti-tau antibody in patients with PSP
- Goal target disorder is AD, but can test first in a pure tauopathy with measurable motor symptoms
- **Pro**: Effect size of treatment may be greater in PSP than AD
- **Cons**: Generalizability to AD

*Not FDA approved for AD.
https://clinicaltrials.gov/ct2/show/NCT03068468?term=progressive+supra+nuclear+palsy&rank=4

Future Direction #3: Treatments Based on Specific Genetic Findings

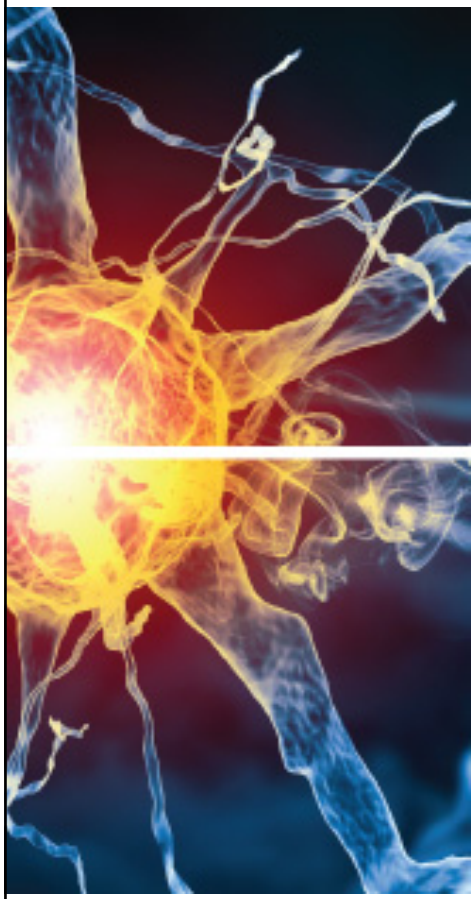
- **Example**: Anti-sense oligonucleotide (ASO) treatments for C9ORF72 mutation carriers with ALS/FTD*
- ASOs selectively target and bind to messenger RNA (mRNA) from the mutated gene
- **Pros**: Targeted therapies
- **Cons**:
  - Specific to a particular mutation
  - AD rarely due to single mutation
  - Some disease mechanisms are not amenable to this type of treatment

*Not FDA approved for AD.

Sha SJ, et al. *Alzheimers Res Ther.* 2012;4(6):46.

SMART Goals: Some Take Home Points

- Not all dementia targets memory and not all MCI is AD
- Current treatments for AD are warranted, but not worth tolerating significant adverse effects
- Low dose antipsychotic meds in dementia, but may need usual doses of antidepressants
- When treating agitation in dementia, continue to evaluate need for medication and non-pharmacologic interventions



Questions & Answers