# Drugs and Dementia (Memory Enhancers?)

Eric Metterhausen, PharmD, BCPS, CPP, CPH

CDR USPHS

Indian Country ECHO

(Special thanks to Rebecca Augustin PharmD candidate for research assistance)

# What Medications may Help Memory in Alzheimer's Disease?

- Removal of exacerbating medications (another topic previously presented, possibly the most effective)
- Cholinesterase inhibitors (donepezil, galantamine, rivastigmine)
- NMDA receptor antagonist (memantine)
- Recombinant monoclonal antibody against amyloid beta
- Anti amyloid
- Vitamin E
- Apoaequorin
- Aspirin
- Fish Oil
- Others with limited data (selegiline, estrogen replacement, statins, NSAIDs, etc)

# Cholinesterase Inhibitors

- Reduced cerebral cholinergic function in AD
- Reversibly inhibit cholinesterase leading to increased cholinergic activity in synaptic cleft
- Examples
  - Donepezil 5-10mg (up to 23mg) oral daily
  - Galantamine (IR and ER) titrated up from 8mg to 24mg oral daily
  - Rivastigmine titrated up from 3mg up to 12mg/day (patch also available up to 13.3mg patch/24hrs)
- FDA approved for mild to severe AD
- Symptomatic treatment, not a cure

Epperly T, Dunay MA, Boice JL. Alzheimer Disease: Pharmacologic and Nonpharmacologic Therapies for Cognitive and Functional Symptoms. Am Fam Physician. 2017 Jun 15;95(12):771-778. PMID: 28671413.

# Cholinesterase Inhibitors Efficacy and Safety

- Have shown statistically significant improvements but are these changes clinically significant
- Donepezil x 2 years lead to 0.8 point improvement in MMSE (30pt scale), no improvement in institutionalization or disability at 3 years.
- Other studies lead to similar cognitive/functional improvements of 2-4 points on a 70 pt scale.
- Benefits not shown to persist after discontinued
- Common side effects – diarrhea, nausea, insomnia
- Serious side effects – QTc prolongation, weight loss, anorexia
- Avoid abrupt withdrawal (agitation, hallucinations) may also see cognitive decline
- Are the benefits worth the risk?
- Importance of baseline testing

Epperly T, Dunay MA, Boice JL. Alzheimer Disease: Pharmacologic and Nonpharmacologic Therapies for Cognitive and Functional Symptoms. Am Fam Physician. 2017 Jun 15;95(12):771-778. PMID: 28671413.

Courtney C, Farrell D, Gray R, et.al; AD2000 Collaborative Group. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. Lancet. 2004 Jun 26;363(9427):2105-15. doi: 10.1016/S0140-6736(04)16499-4. PMID: 15220031.

# N-methyl-D-aspartate (NDMA) receptor antagonist

- Limits glutamatergic excitation protecting cortical and hippocampal neurons
- Memantine – 5mg oral daily titrated to 20mg/day (ER 7mg to 28mg)
- FDA approved for moderate to severe AD
- Symptomatic treatment, not a cure
- Small statistically significant benefit, but generally more tolerable than cholinesterase inhibitors
- Most common side effects: confusion, dizziness, headache
- Can be combined with cholinesterase inhibitors for an additional small benefit

Epperly T, Dunay MA, Boice JL. Alzheimer Disease: Pharmacologic and Nonpharmacologic Therapies for Cognitive and Functional Symptoms. Am Fam Physician. 2017 Jun 15;95(12):771-778. PMID: 28671413.

# Recombinant Monoclonal Antibody against Amyloid Beta

- Reduces amyloid beta plaques
- Aducanumab 1mg/kg IV every 4 weeks titrated up to 10mg/kg
- FDA approved in June 2021 through Accelerated Approval based on reduction of amyloid beta plaques
- Conflicting evidence on if there is a clinical benefit for cognition and if there is it is small
- Possibility of being a disease modifying agent unlike other FDA approved options
- High risk (~40%) of amyloid-related imaging abnormalities (ARIA) which may include microhemorrhage, brain edema, headache, confusion, dizziness
- ~$28,000/year for a 74kg patients
- CMS limiting coverage to patients enrolled in approved clinical trials

https://www.fda.gov/drugs/news-events-human-drugs/fdas-decision-approve-new-treatment-alzheimers-disease

Synnott PG, Whittington MD, Lin GA, Rind DM, Pearson SD. The effectiveness and value of aducanumab for Alzheimer's disease. J Manag Care Spec Pharm. 2021 Nov;27(11):1613-1617. doi: 10.18553/jmcp.2021.27.11.1613. PMID: 34714106.

https://www.cms.gov/newsroom/press-releases/cms-finalizes-medicare-coverage-policy-monoclonal-antibodies-directed-against-amyloid-treatment

# Anti-amyloid

Lecanemab-  is a humanized IgG1 monoclonal antibody that targets soluble aggregated amyloid beta plaques (amyloid protofibrils)[2]

Dosing, per Phase 3 Study, Clarity AD:

- 10 milligram per kilogram (mg/kg) biweekly (once every 2 weeks) administered as i.v. infusion.
- 720 milligram (mg) weekly administered as subcutaneous injection

AE:  ARIA (ARIA-E and/or ARIA-H) was 21.3% in the lecanemab group and 9.3% in the placebo group. [1]

Annual price expected: $9,249-$35,605 “pending sponsor approval”

07/05/22-FDA Accepts and Grants Priority Review, Decision expected 01/06/2023

- Though study results are not yet published, information circulating says “Lecanemab slowed the rate of cognitive decline by 27% at 18 months per CDR-SB.[2]”
- Still awaiting full study results. Small cognitive improvement may not be clinically significant

CMS decision on coverage expected 03/2023.

Eisai and Biogen. (2022, July 13). A Study to Confirm Safety and Efficacy of Lecanemab in Participants With Early Alzheimer's Disease (Clarity AD) - ClinicalTrials.gov. Accessed October 07, 2022, from https://clinicaltrials.gov/ct2/show/record/NCT03887455?term=lecanemab&phase=2&draw=2&rank=2&view=record

LECANEMAB Confirmatory Phase 3 CLARITY AD study met primary endpoint, showing highly statistically significant reduction of clinical decline in large global clinical study of 1,795 participants with early Alzheimer's Disease. Biogen. (2022, September 27). Retrieved October 10, 2022, from https://investors.biogen.com/news-releases/news-release-details/lecanemab-confirmatory-phase-3-clarity-ad-study-met-primary

# Vitamin E

- Neuroprotective
- Vitamin E 2000 international units per day
- May lead to a slower decline in functional status
- Some controversy as to whether there may be worsening mortality with Vitamin E usage

Epperly T, Dunay MA, Boice JL. Alzheimer Disease: Pharmacologic and Nonpharmacologic Therapies for Cognitive and Functional Symptoms. Am Fam Physician. 2017 Jun 15;95(12):771-778. PMID: 28671413.

# Apoaequorin

- Active ingredient in Prevagen
- Binds to calcium potentially improving calcium dysregulation
- Photogenic reaction in jellyfish
- Preliminary research showed
  - No improvement in verbal learning (except potentially for those who were cognitively normal at baseline)
  - Modest improvement in delayed recall (Cognate International Shopping List)
- Dizziness, headache, and nausea were the most common side effects
- Very limited evidence

Apoaequorin. In: Natural Medicines [database on the Internet]. Somerville (MA): Therapeutic Research Center; publication year [2021]. Available from: https://naturalmedicines.therapeuticresearch.com. Subscription required to view.

# Aspirin

- Low dose aspirin (<300mg/day)
- No statistically significant delayed dementia onset or improved cognitive test scores
- Up to 10 times as likely to have GI side effects
- May still be on patient's profile for other reasons

Veronese N, Stubbs B, Maggi S, Thompson T, Schofield P, Muller C, Tseng PT, Lin PY, Carvalho AF, Solmi M. Low-Dose Aspirin Use and Cognitive Function in Older Age: A Systematic Review and Meta-analysis. J Am Geriatr Soc. 2017 Aug;65(8):1763-1768.

# Omega-3 Fatty Acids

- Limited data
- Some evidence that omega-3 polyunsaturated fatty acids are associated with a decreased risk for MCI
- No decreased association found for AD, dementia or the other fatty acids
- GI complaints the most common side effects

Zhu RZ, Chen MQ, Zhang ZW, Wu TY, Zhao WH. Dietary fatty acids and risk for Alzheimer's disease, dementia, and mild cognitive impairment: A prospective cohort meta-analysis. Nutrition. 2021 Oct;90:111355.

# Investigational Medications

- Many disease modifying treatments being investigated
- Anti-amyloids (Breakthrough Therapy)
  - Donanemab – phase 2 cognition and ADL improvement
- Tau protein aggregation inhibitors
  - LMTM has not shown a benefit
- Receptor for Advanced Glycation End Products antagonist
  - Not promising so far
- Glutamate modulator
- Tyrosine kinase inhibitor
- Levetiracetam (antiseizure medication)
  - Possible benefit for those with epileptiform activity

https://www.alz.org/professionals/health-systems-clinicians/management
Breijyeh Z, Karaman R. Comprehensive Review on Alzheimer's Disease: Causes and Treatment. Molecules. 2020 Dec 8;25(24):5789. doi: 10.3390/molecules25245789. PMID: 33302541; PMCID: PMC7764106.
Mintun MA, et al. Donanemab in Early Alzheimer's Disease. N Engl J Med. 2021 May 6;384(18):1691-1704. doi: 10.1056/NEJMoa2100708. Epub 2021 Mar 13. PMID: 33720637.
Vossel K, et al. Effect of Levetiracetam on Cognition in Patients With Alzheimer Disease With and Without Epileptiform Activity: A Randomized Clinical Trial. JAMA Neurol. 2021 Nov 1;78(11):1345-1354. doi: 10.1001/jamaneurol.2021.3310. PMID: 34570177; PMCID: PMC8477304.

# Summary

- Current treatments have limited benefits
- If significant side effects occur, it is likely best to move away from that medication
- Many medications in development