Dementia Medications: Updates and Current Trends

Tonja M. Woods, PharmD, BCGP
Alzheimer’s Summit/WyCOA
UW School of Pharmacy
June 14, 2017
https://www.uwyo.edu/wycoa/
Learning Objectives

• At the end of this presentation, participants should be able to….

• Identify current pharmacologic therapies available for the treatment of dementia

• Differentiate between medications approved to treat dementia and those not approved

• Appreciate the current challenges in the area of research related to treating dementia
Pharmacologic Therapy

- **Cholinesterase Inhibitors**
  - Donepezil - Aricept®
  - Rivastigmine - Exelon®
  - Galantamine - Razadyne®

- **NMDA Receptor Antagonist**
  - Memantine - Namenda®

- **Combination Product**
  - Donepezil & Memantine - Namzaric®
Donepezil - Aricept®

- Dose: 5 – 10 mg daily, 23mg daily

- Action:
  - Blocks the breakdown of a chemical in the brain called acetylcholine = **INCREASES Ach**
  - Thought to improve memory and cognition

- Adverse effects:
  - Nausea, vomiting, diarrhea, loss of appetite, dizziness, weight loss, bradycardia

- Approved to treat all stages of AD
Rivastigmine - Exelon®

- Dose:
  - Oral: 1.5 mg twice daily, ↑ to 3-6 mg twice daily
  - Take with food
  - Transdermal Patch: 4.6, 9.5, 13.3 mg/day

- Action: inhibits acetyl- and butyrylcholinesterase = INCREASES ACh and BCh

- Adverse Effects:
  - nausea and vomiting, anorexia, fatigue, dizziness, muscle weakness, bradycardia

- Approved to treat mild to moderate AD
Galantamine - Razadyne®

- **Dose:** 4 mg twice daily, ↑ to 12 mg twice daily (ER – once daily)
  - Take with food

- **Action:** selective, competitive, reversible ACh inhibitor, enhances action of acetylcholine on nicotinic receptors = **INCREASES ACh**

- **Adverse Effects:**
  - nausea and vomiting, diarrhea, loss of appetite, weight loss

- **Caution in severe kidney & liver impairment**

- Approved for use in mild to moderate AD
Memantine - Namenda®

- XR Dose: 7mg daily, increase weekly to target dose of 28mg daily. 14mg max if renal impairment

- Action: blocks a brain receptor that is thought to add to the cellular harm associated with AD = BLOCKS glutamate
  - ? Neuroprotection

- Adverse Effects:
  - constipation, confusion, dizziness, headache, hallucinations

- DI: Clearance ↓ by 80% when urinary pH >8; caution with carbonic anhydrase inhibitors, sodium bicarbonate

- “provides additional benefit on cognitive/behavioral symptoms” - FALSE
Non-Pharmacologic Treatment Options

- Vitamin E
- Gingko Biloba
- Omega-3 fatty acids*
- Coenzyme Q-10
- Pomegranate*
- Axona*
- Coconut Oil*
- Coral Calcium
- Vitamin D*
- Resveratrol*
*Off Label Use*

- **Nuedexta®**
  - Combination of dextromethorphan and quinidine
    - Dextromethorphan (DXM) binds to receptors in the brain that are thought to help with behavior.
    - Quinidine serves to increase levels of DXM
  - Approved for treatment of PseudoBulbar Affect
    - *Not been shown to be safe or effective in DEMENTIA patients*
  - Adverse Effects: diarrhea, dizziness, peripheral edema, euphoria
*Off Label Use*

- Nuplazid®
  - Pimavanserin
    - Second generation (atypical) antipsychotic
  - Approved for treatment in Parkinson’s disease psychosis

- Increased mortality in elderly patients with dementia-related psychosis

- Adverse Effects: CNS depression, QT prolongation, orthostatic hypotension, death (cardiovascular related or infection)
CLINICAL RESEARCH

Dementia – What’s Happening?!
Clinical Trials…

• Current treatments only address symptoms

• Goals:
  • Delay progression
  • Halt progression
  • Prevent pathophysiology

• Primary Areas of Research
  • β-Amyloid plaques
  • Tau formation

• Neuroinflammation
Current Agents being studied......

- **Etanercept (Enbrel®)**
  - Disease modifying agent – Rheumatoid Arthritis
    - Blocks Tumor Necrosis Factor (TNF-α)
  - Alzheimer’s (AD) Hypothesis – reduce inflammation and oxidative stress
    - Chronic inflammatory events in the brain associated with onset and progression of AD
    - Oxidative stress implicated in pathogenesis of AD
    - Injected into tissues near spinal column - no significant findings to date.

- **Rasagiline (Azilect®)**
  - MAO-B inhibitor – Parkinson’s Disease
  - Works on chemical in brain that to prevent breakdown of dopamine. In AD research, thought to be powerful antioxidant and improves glucose metabolism in brain.
B-AMYLOID AGENTS
Beta-secretase 1 (BACE1) inhibitors

- **Verubecestat (Merck)**
  - Trial halted in Feb 2017 for mild to moderate AD
    - “virtually no chance” of working
  - Trial still ongoing for early stage AD
    - Results due Feb 2019

- **Solanezumab (Eli Lilly)**
  - Trial halted Nov 2016
  - St. Louis – ongoing with healthy patients at high risk

- **Lanabecestat (AstraZeneca & Eli Lilly)**
  - Agreement to co-develop in 2014, ongoing study with 2,200 patients, results due June 2019
BACE1 inhibitors...

- Aducanumab (Biogen)
  - Studied in patients with amyloid in their brains but were early in disease process

- Elenbecestat (Biogen & Eisai)
  - MISSION AD1 study

- ADVERSE EFFECTS: risk of hemorrhagic stroke, fluid shifts in brain resulting in swelling
OTHER AGENTS
T-type calcium channel enhancer

- SAK3
  - Japanese research group – January 2017
  - Stimulates release of acetylcholine
  - Reduces production of amyloid-beta
  - “first disease-modifying drug to prevent mild to severe Alzheimer’s disease”
Antisense Oligonucleotides (ASOs)

• Mechanism of action:
  • Reduce levels of existing tau
  • Prevent tau formation
  • Decrease brain inflammation

• Limitation:
  • Much of research has been conducted in brains with pure tau disorders and no amyloid deposition
  • Need improved dosage form – can only be given directly into brain ventricles at this time
5HT6 receptor antagonist

- Intepirdine (Axovant®)
  - Block 5HT6 receptor to increase release of acetylcholine

- Adjunctive use with donepezil
  - Increase Ach without worsening side effects associated with cholinesterase inhibitors such as nausea and vomiting
Persevere 1
Success 2
Questions?