ALZHEIMER’S DISEASE
PHARMACOLOGY

University of Hawai‘i Hilo Pre-Nursing Program
NURS 203 – General Pharmacology
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LEARNING OBJECTIVES

- Understand how the proposed hypotheses for Alzheimer’s Disease explains the drugs used to treat the symptoms
- Know which drugs belong to which class in the treatment of Alzheimer’s disease
- Understand the pharmacologic differences between cholinesterase inhibitors that give individual drugs a place in therapy
- Know the pharmacologic characteristics of NMDA inhibitors and how they work for Alzheimer’s Disease
OVERVIEW

- Review of Alzheimer’s Disease
- Hypotheses surrounding Alzheimer’s Disease
- Drugs used to treat Alzheimer’s disease
WHAT IS ALZHEIMER’S DISEASE?

- Neurodegenerative disease associated with
  - Impaired memory
  - Difficulty recognizing people, stimuli, & objects
  - Impaired writing & speech abilities
  - Depression, aggression, moodiness
  - Impaired motor skills

1. Plaques
2. Neurofibrillary tangles
3. Atrophy of brain areas
4. Decrease in acetylcholine
5. Excessive glutamate
1. Alpha secretase
   - Neuronal growth
   - Neuronal survival
   - Synaptic health

2. Beta secretase
   - Axon health through selective apoptosis (DR6 receptor)

3. Gamma secretase
   - Formation of plaques
     - Inflammation
     - Death receptor activation
     - Reactive oxygen species

Amyloid Precursor Proteins

sAPP

N-APP

Aβ

UNDER NORMAL CIRCUMSTANCES
WHAT MIGHT BE HAPPENING IN AD - PLAQUES

1. Alpha secretase
   - Neuronal growth
   - Neuronal survival
   - Synaptic health

2. Beta secretase
   - Axon health through selective apoptosis (DR6 receptor)

3. Gamma secretase
   - Formation of plaques
     - Inflammation
     - Death receptor activation
     - Reactive oxygen species

sAPP

N-APP

Aβ

Too much N-APP
Excessive apoptosis

Too much Aβ
Aggregates
Forms Plaques
Under normal circumstances

- Tao – Protein involved in the stabilization of microtubules

Alzheimer’s Disease

WHAT MIGHT BE HAPPENING IN AD - TANGLES
Under normal circumstances

- Tao – Protein involved in the stabilization of microtubules

Alzheimer’s Disease

1. Acetylcholine
2. Aβ
3. Glutamate (NMDA receptor)

WHAT MIGHT BE HAPPENING IN AD - TANGLES
WHAT MIGHT BE HAPPENING IN AD – PLAQUES & TANGLES

Cholinergic deficits

1. Acetylcholine
2. Aβ
3. Glutamate (NMDA receptor)

Glutamate excess

Glutamate

Na & Ca

Acetylcholine

ATP depletion

Activation of the Calpain enzyme

Apoptosis

Enzyme
<table>
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<tr>
<th>Cholinesterase Inhibitors</th>
<th>NMDA Antagonists</th>
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<td>Tacrine (Cognex)</td>
<td>Memantine (Namenda)</td>
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<td>Donepezil (Aricept)</td>
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<td>Rivastigmine (Exelon)</td>
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CHOLINESTERASE INHIBITORS
- MOA – Centrally active reversible inhibitor of acetylcholinesterase
- Dosage forms – oral
- Kinetics
  - High first pass effect - ~17% oral bioavailability
  - Food decreases drug concentrations
  - Metabolism – CYP1A2, has an active metabolite
  - Half-life – 2-4 hours
  - Excretion - urine

- ADRs
  - Nausea, vomiting, diarrhea, weight loss, dizziness, headache
  - Severe: hepatotoxicity

- Interactions
  - Antipsychotics (increase in EPS), inhibitors of CYP1A2 (fluoroquinolones, antifungals, cimetidine, fluvoxamine)
  - Bioavailability reduced by food
CHOLINESTERASE INHIBITORS - DONEPEZIL

- MOA – Reversible and noncompetitive inhibitor of central acetylcholinesterase
- Dosage forms
  - Oral – 10 mg & 23 mg tablet, ODT 5mg & 10 mg
- Kinetics
  - Absorption – well absorbed
  - Distribution – large Vd, lipophilic
  - Protein binding – 96%
  - Metabolism – extensive via CYP2D6 & 3A4, metabolites (inactive & active)
  - Half-life – 70 hours (15 days to steady state)
  - Time to peak – 3 hours, 8 hours
  - Excretion – urine 57% (17% unchanged drug), feces 15%
- ADRs
  - Insomnia, nausea, vomiting, diarrhea, infection, accidental injury, headache, dizziness, weight loss, fatigue, arrhythmia, rhabdomyolysis
- Interactions
  - Anticholinergic & cholinergic medications, beta blockers, inhibitors of CYP2D6 & 3A4, statins
  - Pregnancy category - C
  - Breast milk – not known
MOA – Reversible inhibition of the hydrolysis of acetylcholine by cholinesterase

Dosage forms
- Oral – tablet & solution
- Transdermal patch

Kinetics
- Absorption – oral, rapid & complete (fasting), transdermal 30-60 minutes
- Protein binding – ~40%
- Metabolism – hydrolysis by cholinesterase in the brain, demethylation & conjugation in the liver (minimal CYP)
- Half-life – oral 1.5 hours, patch ~ 3 hours upon removal
- Time to peak – oral 1 hour, patch 6-8 hours after applied
- Excretion – urine (97% metabolites)

ADRs
- Headache, agitation, falling, weight loss, nausea, vomiting, diarrhea, abdominal pain, tremor, fatigue, insomnia, confusion, dyspepsia, UTI
- Transdermal
  - decreased incidence of ADRs overall
  - Redness at application site

Interactions
- Avoid use with beta blockers (other agents that can cause bradycardia), avoid use with metoclopramide, cholinergic agents & anticholinergic agents, antipsychotic agents (severe EPS)
- Pregnancy category – B
- Breast milk – not known
- Food delays absorption but increases bioavailability

CHOLINESTERASE INHIBITORS - RIVASTIGMINE
• MOA – Competitive & reversible central cholinesterase inhibitor, **may also increase glutamate & serotonin levels**

• Dosage forms
  - Oral – solution & tablet (IR & ER)

• Kinetics
  - Distribution – large
  - Protein binding – low
  - Metabolism – CYP2D6 & 3A4 (minor)
  - Bioavailability – 90%
  - Half-life – 7 hours
  - Time to peak – 1 hour (2.5 with food), 4.5-5 hours
  - Excreted – urine (20%)

• ADRs
  - **Nausea**, vomiting, headache, diarrhea, weight loss

• Interactions
  - Anticholinergics & cholinergic agents, antipsychotics, beta blockers & other agents that slow heart rate (**high incidence of interaction with drugs that prolong QT interval**)  
  - Pregnancy category – C
  - Breast milk – not known

**CHOLINESTERASE INHIBITORS - GALANTAMINE**
MOA – noncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptor for glutamate, decreases glutamate activity under conditions of excessive excitation (does not effect normal neurotransmission), antagonized 5HT & nicotinic receptors, agonist at DA receptors

Dosage forms
- Oral – solution & tablet (IR&ER)

Kinetics
- Absorption – well absorbed
- Protein bound - ~45%
- Metabolism – Liver (not CYP), minor - inactive metabolites
- Half-life – 60-80 hours
- Time to peak – 3-7 hours, 9-12 hours (IR/ER)
- Excretion – urine (unchanged)

ADRs
- Hypertension & hypotension (IR/ER), dizziness, confusion, headache, anxiety, diarrhea, constipation

Interactions
- Minor
- Pregnancy category – B
- Breast milk – not known

NMDA ANTAGONISTS - MEMANTINE