YOU KNOW THE SEMESTER HAS REALLY STARTED WHEN...

YOUR PHONE AUTO-CORRECTS "A LOT" TO "AORTA"

PHARMACOLOGY

Drugs for Alzheimer's Disease

Skye McKennon, PharmD. BCPS, ACSM-GEI

WASHINGTON STATE UNIVERSITY
Elson S. Floyd College of Medicine

DISCLOSURE

None

Use Statement

OBJECTIVES

1. Identify the appropriate drugs and drug classes for managing Alzheimer's disease
2. Explain the mechanism of action of cholinesterase inhibitors, N-methyl-D-aspartate (NMDA) receptor antagonists, and amyloid beta-directed monoclonal antibodies and correlate to the underlying pathophysiology of Alzheimer's disease
3. Describe adverse effects and contraindications to cholinesterase inhibitors, N-methyl-D-aspartate (NMDA) receptor antagonists, and amyloid beta-directed monoclonal antibodies
4. Describe the clinically important drug interactions of cholinesterase inhibitors, N-methyl-D-aspartate (NMDA) receptor antagonists, and amyloid beta-directed monoclonal antibodies

ACTIVE LEARNING

Describe the pathophysiology and neurochemistry of Alzheimer's disease.

ABBREVIATED PATHOPHYSIOLOGY OF AD

Pathological hallmarks are amyloid plaques

1. Extracellular accumulations of Aβ
2. Intracellular neurofibrillary tangles composed of microtubule-associated protein tau
   - Aβ and tau induce neuronal dysfunction and death via direct impairment of synaptic transmission and plasticity, excitotoxicity, oxidative stress, and neuroinflammation

Thought to result from multiple mechanisms including, but not limited to:

- Progressive loss of neurons, especially **cholinergic neurons**
- Overactive glutaminergic systems resulting in neurotoxicity

NEUROCHEMISTRY OF AD – ACETYLCHOLINE

Most striking neurohormonal disturbance is deficiency in acetylcholine (ACh)

- Atrophy and degeneration of subcortical cholinergic neurons

Selective deficiency of ACh in AD and the observation that central cholinergic antagonists (e.g., atropine) can induce a confusional state resembling the dementia of AD given rise to the "cholinergic hypothesis"

ACh deficiency critical in genesis of AD symptoms

NEUROCHEMISTRY OF AD – OTHERS

AD involves multiple neurotransmitter systems, including glutamate, 5HT, and neuropeptides

- Destruction of cholinergic neurons but also of cortical and hippocampal targets that receive cholinergic input

ACTIVE LEARNING

Based on its pathophysiology, list three potential pharmacologic targets for the management of AD.

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CHOLINESTERASE INHIBITORS

ACETYLCHOLINESTERASE

Acetylcholinesterase (AChE) is a cholinergic enzyme

- Breaks down or hydrolyzes acetylcholine (ACh) into acetic acid and choline
- Primarily found at postsynaptic neuromuscular junctions (esp in muscles and nerves)

AChE terminates neuronal transmission and signaling between synapses to prevent ACh dispersal and activation of nearby receptors

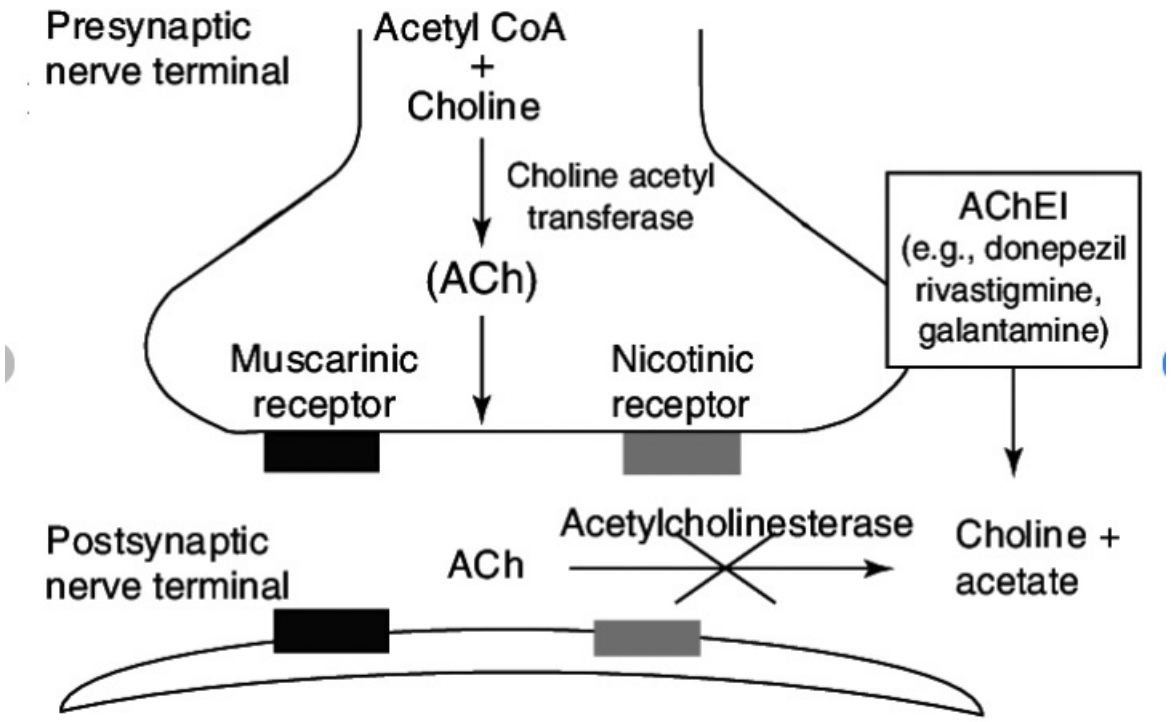
AChE inhibited by organophosphates (components of pesticides and nerve agents)

CHOLINESTERASE INHIBITOR MECHANISM OF ACTION

Reversible antagonists of AChE

- Prevents the degradation of ACh to choline and acetate
- Increases concentration, half-life, and actions of ACh in synapses where ACh is released physiologically

No significant actions at non-innervated sites (where ACh is not normally released, eg, vascular endothelial cells)



CHOLINESTERASE INHIBITORS

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Donepezil Rivastigmine Galantamine	Cardiac conduction abnormalities Uncontrolled epilepsy Unexplained syncope Active peptic ulcer disease	**Nausea** **Muscle cramping** **Dizziness** **Insomnia, abnormal dreams**	May enhance the QTc-prolonging effect of QT-prolonging agents

CLINICAL USE & ADME

Mild or moderate dementia due to AD

Off label

- Other neurodegenerative diseases with cholinergic deficits
  - Dementia with Lewy bodies
  - Vascular dementia

Donepezil and rivastigmine noncompetitive

- Galantamine is competitive

Donepezil and galantamine metabolized by CYP2D6 and CYP3A4

- Rivastigmine metabolized by esterases

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NMDA RECEPTOR ANTAGONISTS

NMDA RECEPTOR ANTAGONIST MECHANISM OF ACTION

NMDA-type glutamate receptor

- NMDA receptor activated by glutamate
  - Glutamate is principal **EXCITATORY** neurotransmitter in cortical and hippocampal neurons
- Overstimulation of glutamate receptors may lead to excitotoxicity and neuronal cell death

Antagonizing NMDA receptor may be neuroprotective

Noncompetitive antagonist of the NMDA-receptor subtype of glutamate receptors

NMDA RECEPTOR ANTAGONIST

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Memantine (Namenda)	Cautions: Increased incidence of cardiac failure, bradycardia, and hypertension/hypotension May increase risk of seizures Renal or hepatic impairment	Confusion Dizziness Headache Agitation, delusion, hallucination	Carbonic anhydrase inhibitors may increase serum concentrations

CLINICAL USE & ADME

Moderate to severe AD

Off label

- Dementia (Parkinson disease, Lewy bodies, vascular)
- Prevention of neurocognitive toxicity of whole brain irradiation

Well absorbed orally

Metabolized hepatically

- Primarily independent of the CYP system

ACTIVE LEARNING

Biologic products are created with biotechnology and encompass blood components, somatic cells, gene therapy, tissues, recombinant proteins, and vaccines. They are derived from microorganisms, plant, animal, or human cells.

Monoclonal antibodies are a large subset of biologics.

Aducanumab is a monoclonal antibody used to treat Alzheimer Disease. Based on its name, what is the target and source species of aducanumab?

MONOCLONAL ANTIBODY NOMENCLATURE

Name Component	Meaning
Prefix	Random, should contribute to distinctive name
Substem A	Target class
Substem B	Species
Suffix	-mab (for **m**onoclonal **a**nti**b**ody)

Target Class	Substem A
Bacterial	-b(a), -ba(c)
Serum amyloid protein	-am(i)
Cardiovascular	-c(i), -ci(r)
Fungal	-f(u), -fung
Skeletal muscle related growth factors	-gr(o)
Interleukin	-k(i), -ki(n)
Immunomodulating	-l(i), -li(m)
Neural	-n(e)
Bone	-s(o), -os
Toxin	-tox(a)
Tumor	-t(u)
Viral	-v(i), -vi(r)

Source Species	Substem B
Rat	a
Rat/mouse	axo
Hamster	e
Primate	i
Mouse	o
Human	u
Chimeric	xi
Chimeric/humanized	xizu
Humanized	zu

ADUCANUMAB

Name Component	Meaning	Adalimumab Example	
Prefix	Random, should contribute to distinctive name	Aduca	Random
Substem A	Target class	-n	Neuro
Substem B	Species	-u	Human
Suffix	-mab (for **m**onoclonal **a**nti**b**ody)	-mab	Monoclonal antibody

ACTIVE LEARNING

Adalimumab and infliximab are two monoclonal antibodies. Based on their names, what is the target and source species of adalimumab and infliximab?

Ustekinumab (Stelara) is commonly used monoclonal antibody. Based on its name, what is the target and source species?

ADALIMUMAB

Name Component	Meaning	Adalimumab Example	
Prefix	Random, should contribute to distinctive name	Ada	Random
Substem A	Target class	-lim	immunomodulating
Substem B	Species	-u	Human
Suffix	-mab (for **m**onoclonal **a**nti**b**ody)	-mab	Monoclonal antibody

INFLIXIMAB

Name Component	Meaning	Adalimumab Example	
Prefix	Random, should contribute to distinctive name	Inf	Random
Substem A	Target class	-li	immunomodulating
Substem B	Species	-xi	Chimeric
Suffix	-mab (for **m**onoclonal **a**nti**b**ody)	-mab	Monoclonal antibody

USTEKINUMAB

Name Component	Meaning	Adalimumab Example	
Prefix	Random, should contribute to distinctive name	Uste	Random
Substem A	Target class	-kin	interleukin
Substem B	Species	u	Humanized
Suffix	-mab (for **m**onoclonal **a**nti**b**ody)	-mab	Monoclonal antibody

Ustekinumab (Stelara) is a fully human monoclonal antibody that targets interleukin-12 and -23

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AMYLOID BETA-DIRECTED MONOCLONAL ANTIBODIES

AMYLOID BETA-DIRECTED MAB MOA

Recombinant monoclonal antibody directed against amyloid beta

Crosses blood-brain barrier

Selectively targets and binds aggregated soluble oligomers and insoluble fibril conformations of Aβ plaques in the brain

Demonstrated reduction of surrogate endpoint of ↓ amyloid beta plaques in the brain

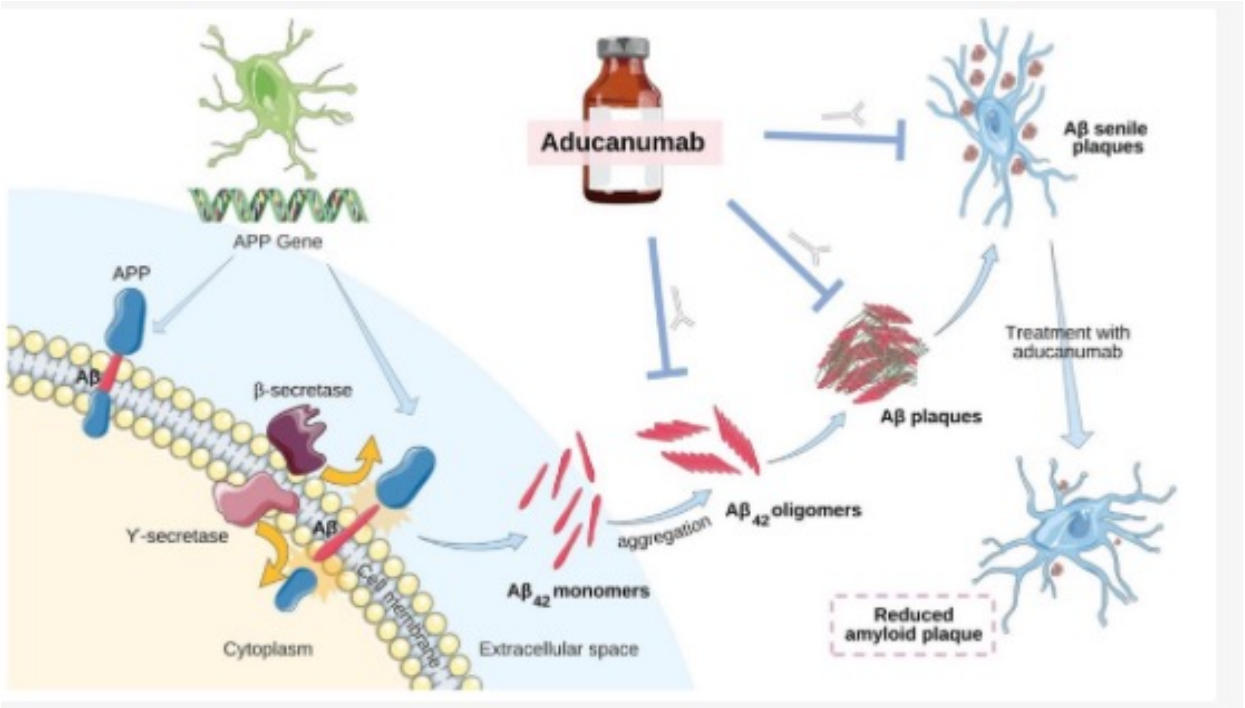

Image credit: https://www.mdpi.com/2076-3425/11/11/1547

AMYLOID BETA-DIRECTED MAB

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Aducanumab (Aduhelm)	Confirm the presence of amyloid beta pathology prior to treatment initiation Caution: high risk of hemorrhagic side effects	Amyloid-related imaging abnormalities (ARIAs) – edema, microhemorrhages	May diminish the therapeutic effect of Fc Receptor-Binding Agents (efgartigimod Alfa, rozanolixizumab)

CLINICAL USE & ADME

AD at the mild cognitive impairment or mild dementia stage

Monthly intravenous infusion

REFERENCE LIST

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ANY QUESTIONS?