Alzheimer's Disease (AD)

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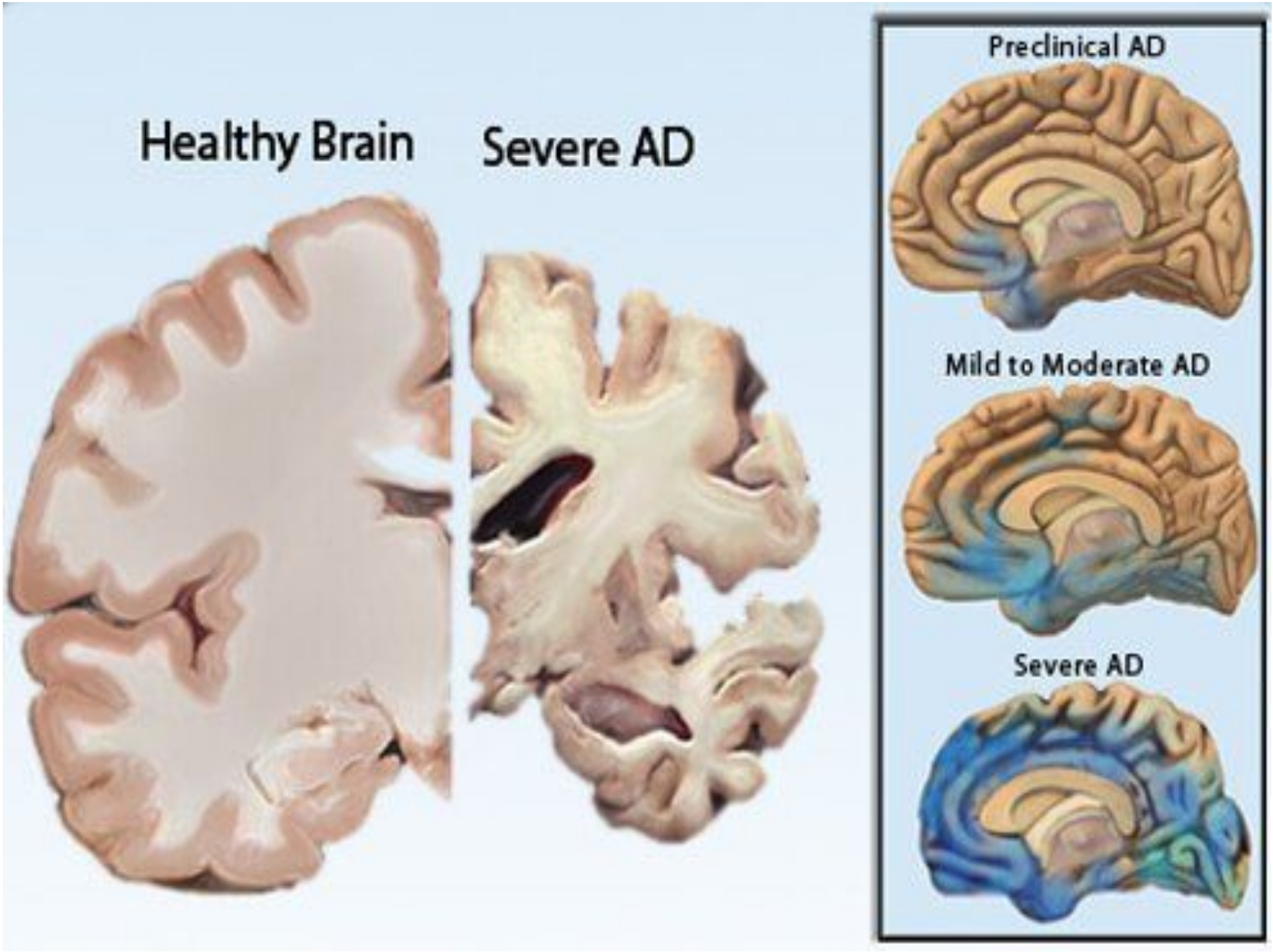
Drugs Used in Alzheimer's Disease

Dementia of the Alzheimer's type (versus the other forms of dementia such as multi-infarct :dementia has three distinguishing features

accumulation of senile **plaques** (amyloid (1 ,accumulations)

formation of numerous neurofibrillary **tangles** (2

loss of cortical neurons(particularly (3 .**cholinergic** neurons)


Healthy Brain
Severe AD
Preclinical AD
Mild to Moderate AD
Severe AD

Therapies are aimed at either

improving cholinergic transmission within the **-1** CNS or

preventing excitotoxic actions resulting from **-2** overstimulation of N-methyl-D-aspartic acid (NMDA)-glutamate receptors in selected brain areas.

: **Thus** drugs used in treatment include

A. Acetylcholinesterase inhibitors

inhibition of acetylcholinesterase (AChE) within the CNS will improve cholinergic transmission, at least .at those neurons that are still functioning

Currently, four **reversible AChE inhibitors** are approved for the treatment of mild to moderate Alzheimer's

Donepezil, galantamine, rivastigmine and
. tacrine

galantamine (**also act as modulator** of the **nicotinic** receptor in the CNS)

all are **uncompetitive** inhibitors of AChE **except** galantamine (**competitive**)

all have some **selectivity** for AChE in the **CNS** as compared to the periphery

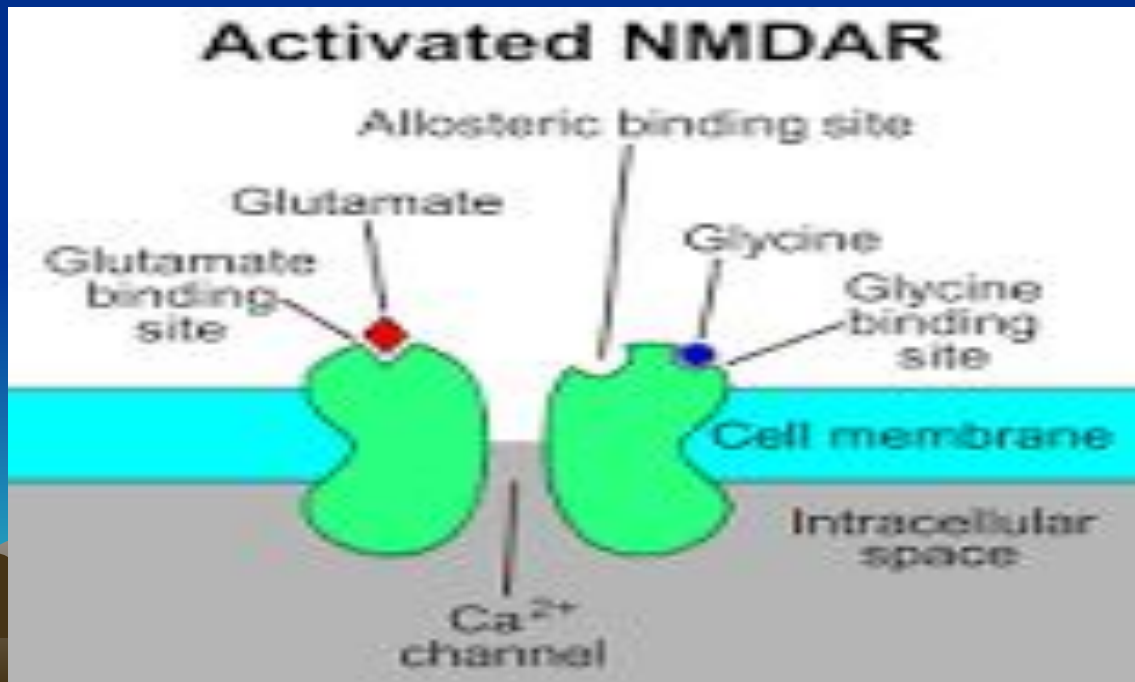
Rivastigmine has **no interactions** with drugs that .alter the activity of P450-dependent enzymes

The **other** agents are a potential for such .**interactions**

B. NMDA-receptor antagonist

Stimulation of glutamate receptors in the CNS appears to be critical for the formation of certain **memories**; however, **overstimulation** of glutamate receptors, particularly of the NMDA type, has been shown to result in **excitotoxic** effects on neurons and is suggested as a mechanism for **neurodegenerative** or apoptotic (programmed cell death) .processes

Binding of **glutamate** to the **NMDA** receptor assists in the **opening** of an associated ion channel that allows **$Na^{\pm}$** and, particularly, **Ca^{2+}** to enter the neuron. Unfortunately, **excess** intracellular **Ca^{2+}** can activate a number of processes that ultimately **damage** neurons and lead to apoptosis



Memantine (**blocking NMDA**), well tolerated

only a fraction of **channels** are actually **blocked** allowing memantine to **limit Ca^{2+} influx** (still **permitting sufficient Ca^{2+}** flow through unblocked channels to preserve other vital processes that depend .on Ca^{2+} (or Na^{+}) influx

in contrast to **psychotoxic** agents such as phencyclidine, which **block** nearly **all** of these channels

memantine prevents or **slows** the **neurodegeneration** .is **more effective** than the **AChE** inhibitors

THANK YOU