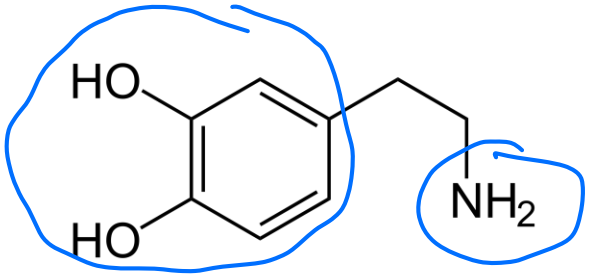
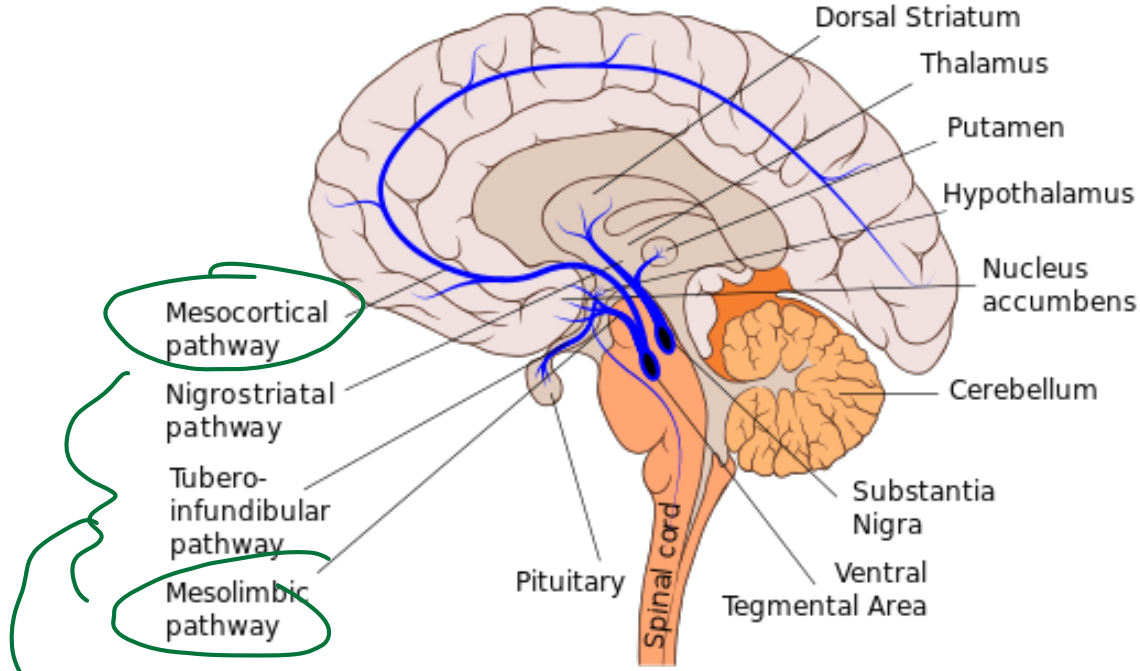
Dopamine Receptors



Dopamine

Catecholamine



Low DA levels

Parkinson's

hypokinesia

Dystonias

high DA levels

hyperkinesia

hyperactivity

Tourettes

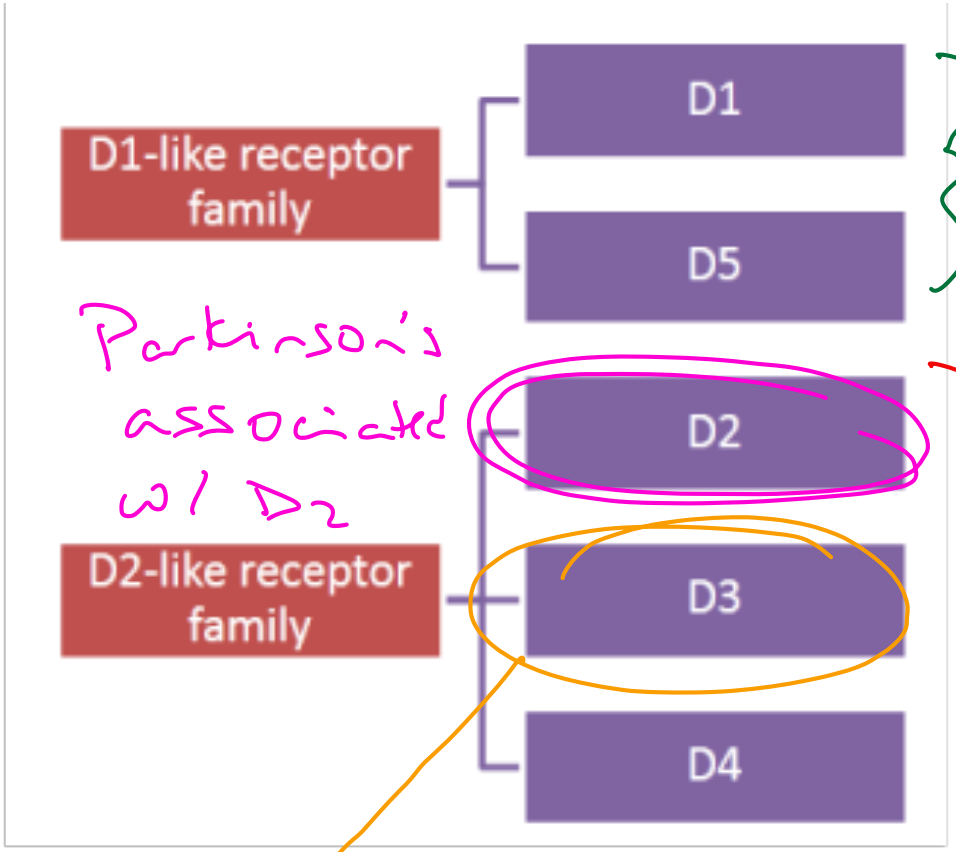
associated with reward effects of drugs + food

Dopamingergic Neural Pathways

	Project to	Function of Dopamine	Diseases due to ↑DA	Diseases due to ↓DA	Dopamine antagonists	Dopamine agonists
Nigrostriatal Tract	Striatum	Inhibits GABA-ergic neurons		**Parkinsonism:** extrapyramidal dysfunction	Pseudo-parkinsonism (reversible)	Dyskinesias
Mesolimbic-mesocortical tracts	Cerebrocortical and limbic structures	• Regulation of affect • Reinforcement • Cognitive functions • Sensory perception	• Psychotic disorders (schizophrenia) • Addiction		↓cognitive function	Reinforcement Psychoses
Tuberoinfundibular tract	Anterior pituitary	↓Prolactin secretion			Endocrine dysfunction including gynecomastia and amenorrhea/galactorrhea	↓prolactin levels (used in hyperprolactinemic states) e.g. pergolide
Chemoreceptor trigger zone		Emesis when stimulated			Antiemetic	Emetic e.g. apomorphine

5 subclasses

All GPCR's (metabotropic)



increase cAMP concentration post synaptic

Parkinson's associated w/ D2

decrease cAMP conc. post + pre synaptic

genes have multiple splicing patterns

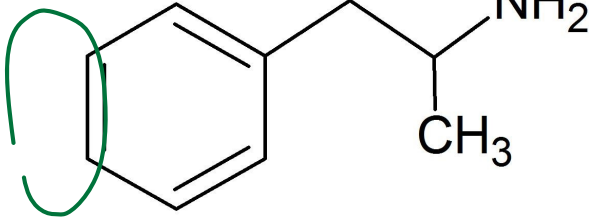
Drug addiction associated with D_3

D2S pre

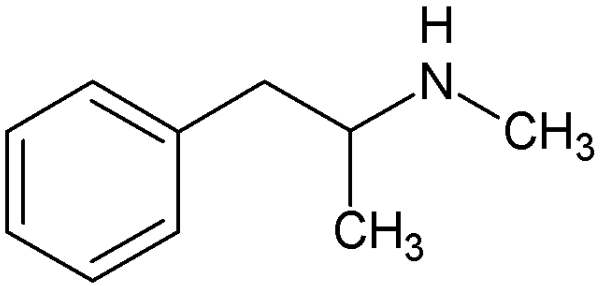
D2L post

Dopamine Agonists

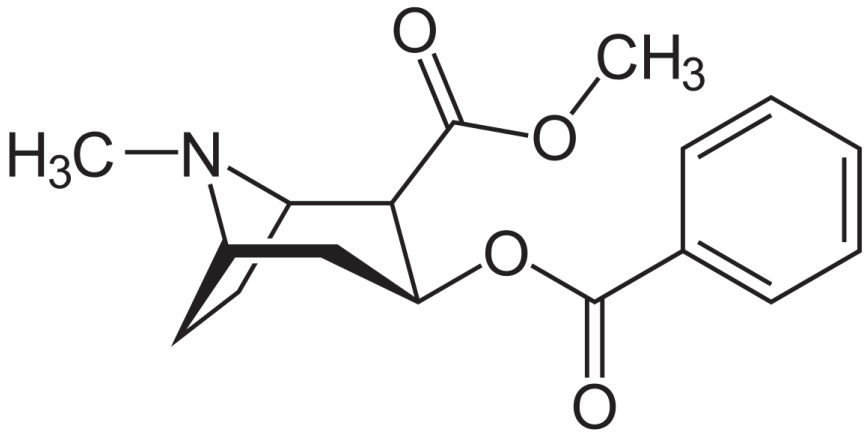
Amphetamine

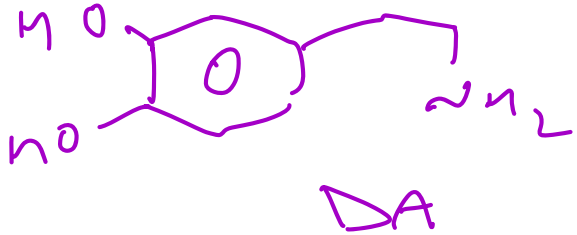


methamphetamine



Cocaine

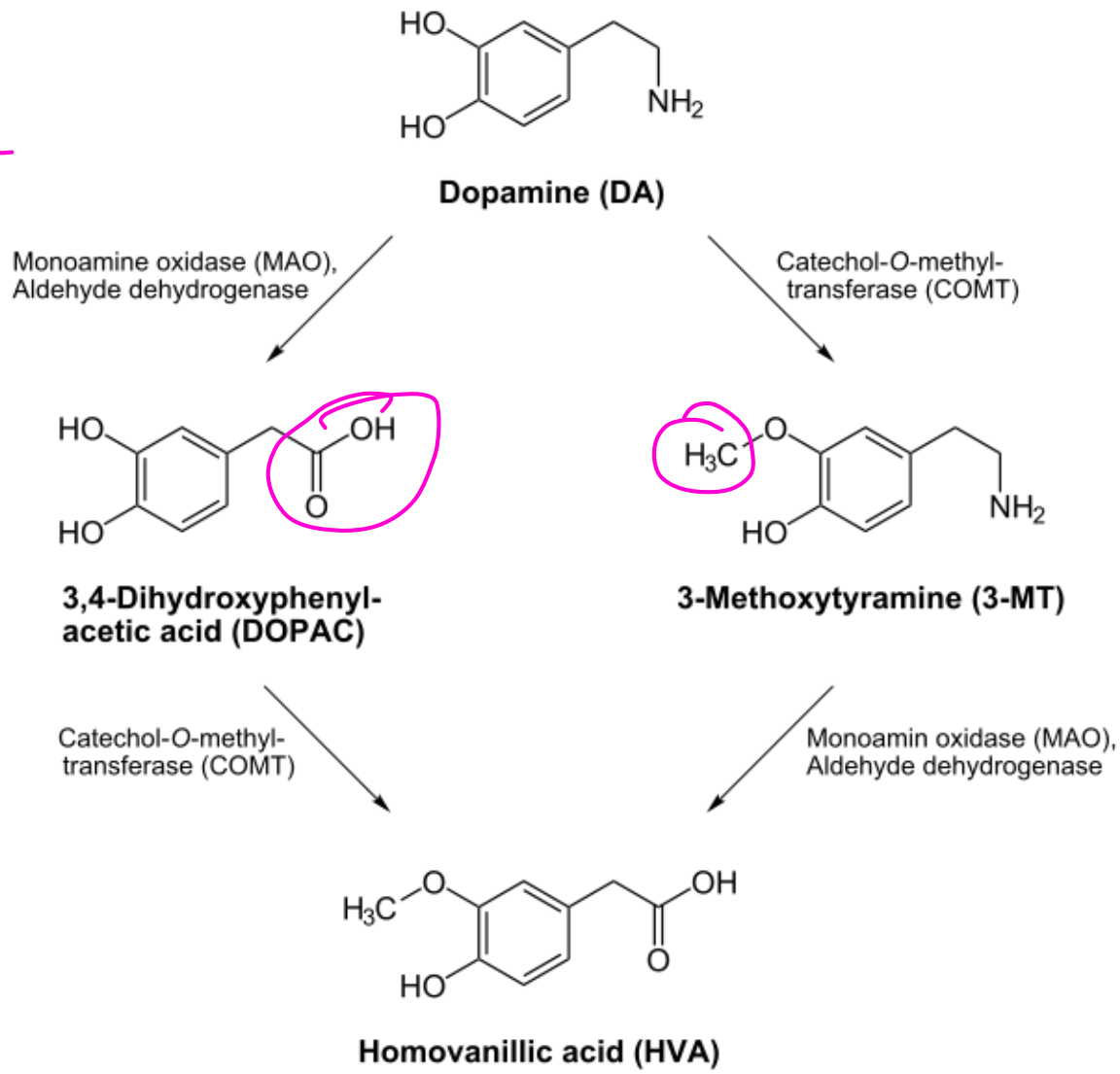




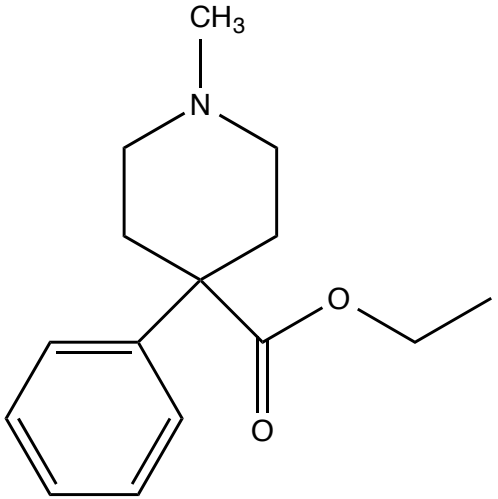
DA

DA is a catecholamine

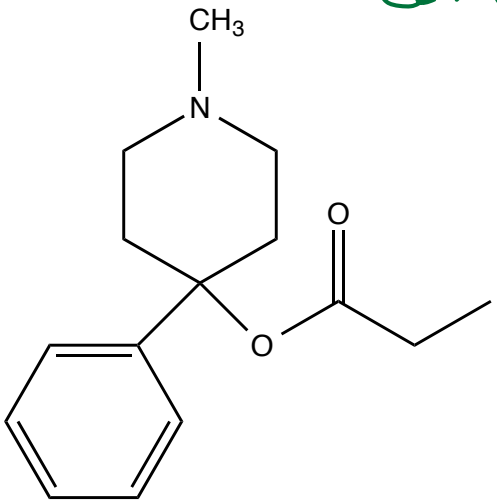
use MAO COMT

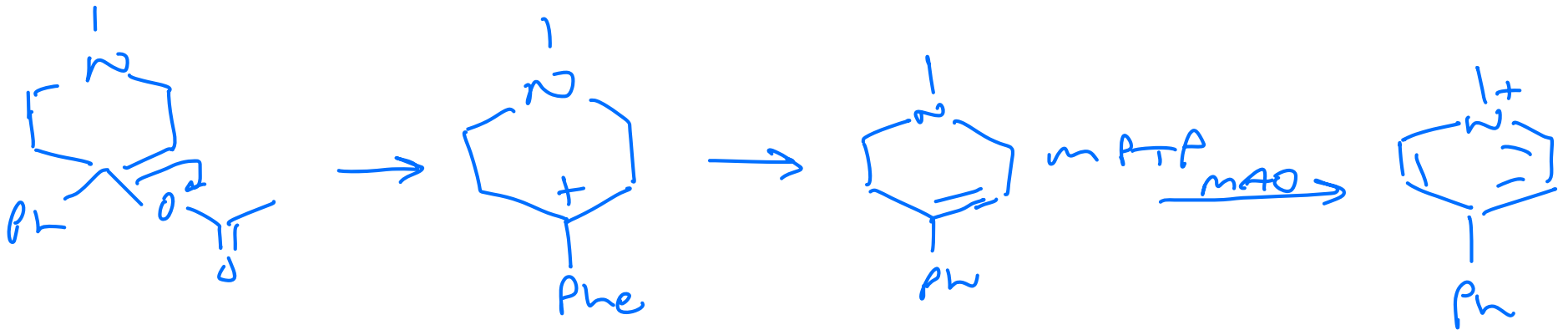


meperidine



designer heroin (reverse ester)



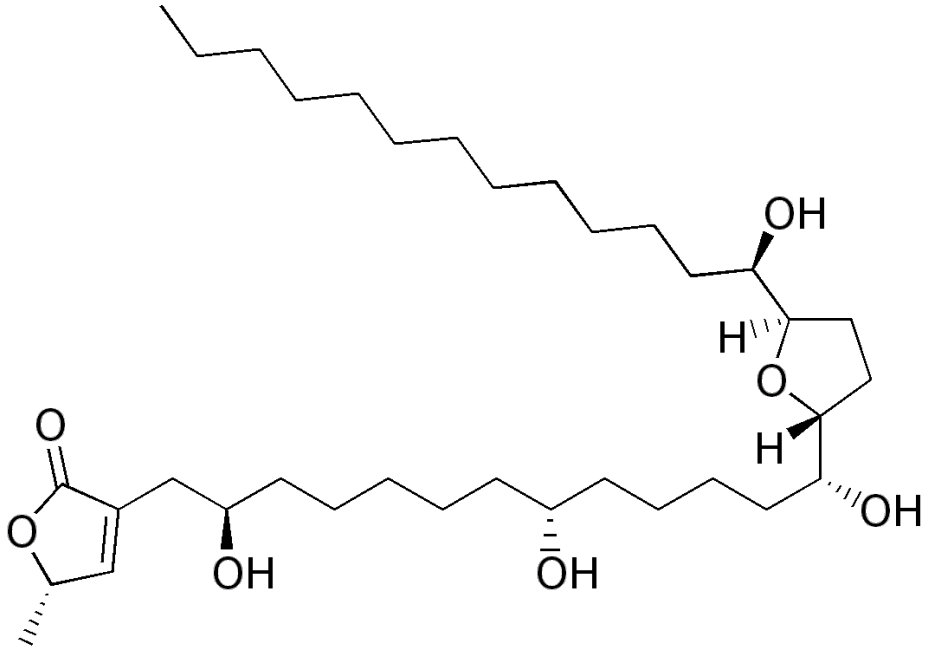


* treated patients with MAO I's to stop formation of inhibitor

Complex I inhibitor

Caused cell death in substantia

nigra



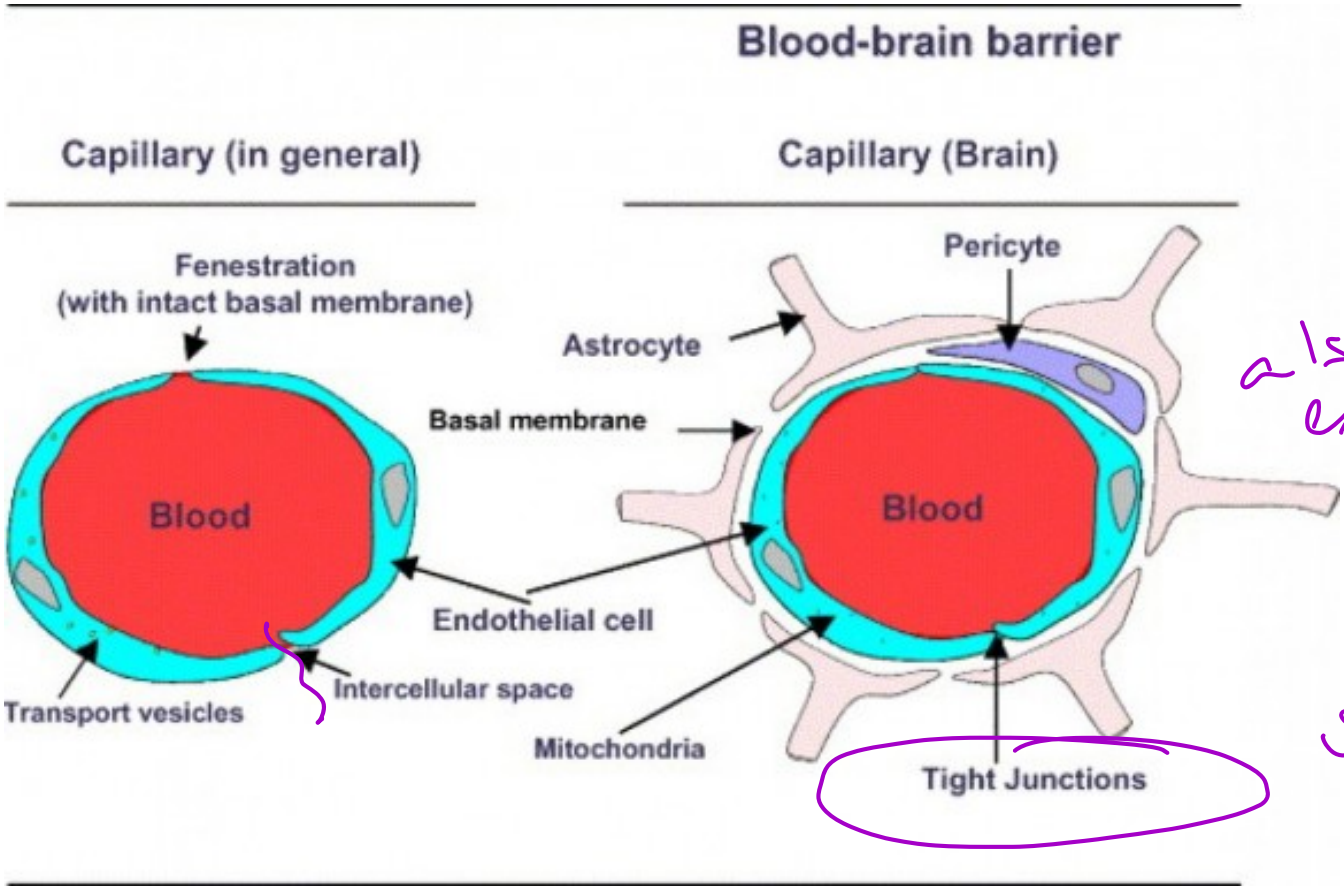
Complex I inhibitor

annonacin

found in soursop
(pao pao)

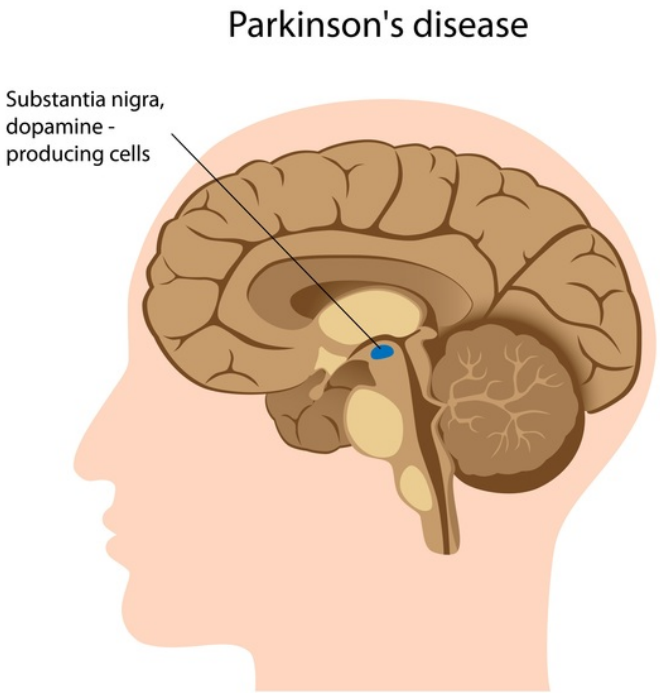
high consumption
linked to PD

Getting drugs in is hard



also extra lipid layer

vascular tissue makes enzymes like esterases that make things polar ish



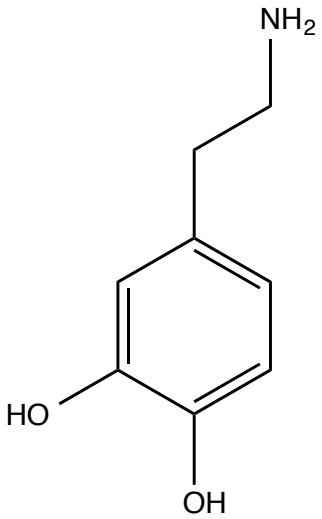
PD have lowered levels of DA

Probably due to oxidative stess that iniates in mitochondria

Rigidity
Tremors
Gait changes
Speech / swallowing difficulty

Depression
Sleep Disorders

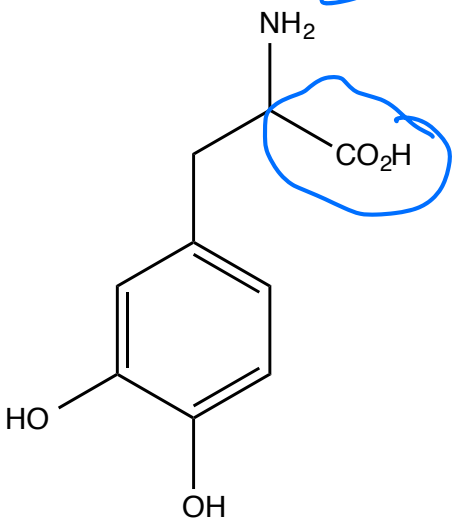
Dopamine



pKa 10.6
at pH=7
protonated not
lipid soluble

Levodopa

L-Dopa



pKa 8.7
more in deprotonated form
more lipid soluble

taken up by amino acid transporters

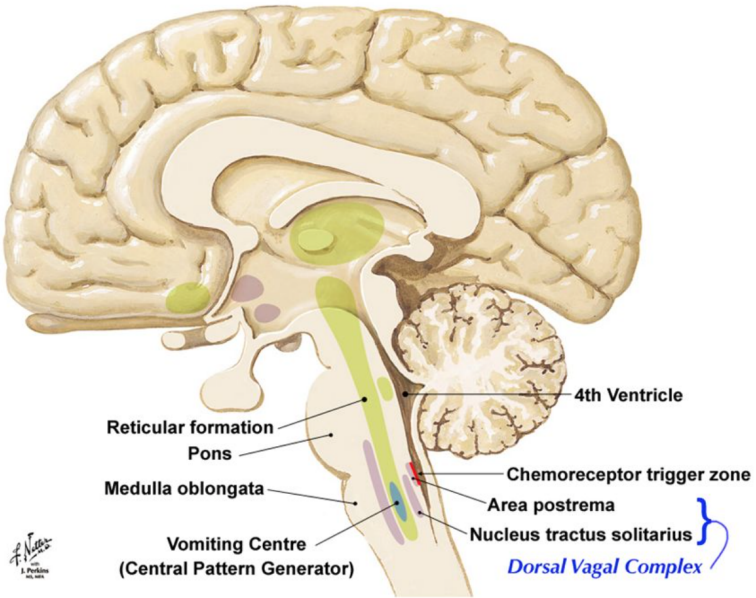
Levodopa and Adrenergic Receptors

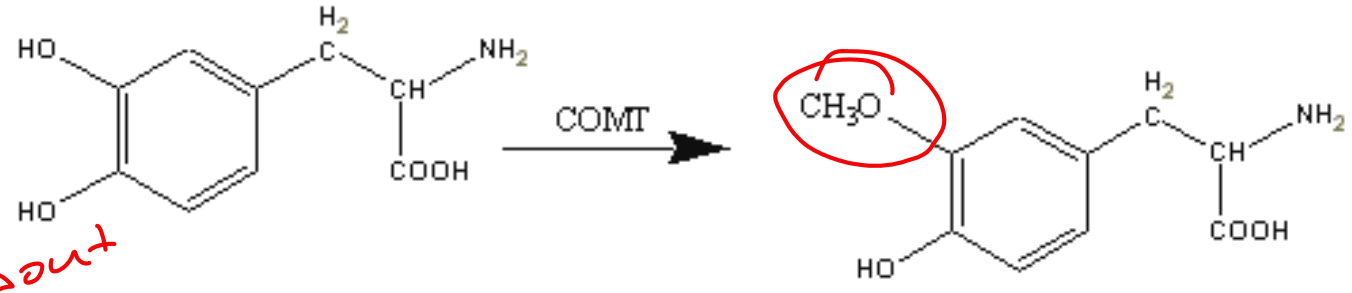
Catechol similar to NE

β – increase in heart rate

α – Vasoconstriction

CTZ chemoreceptor trigger zone





Levodopa

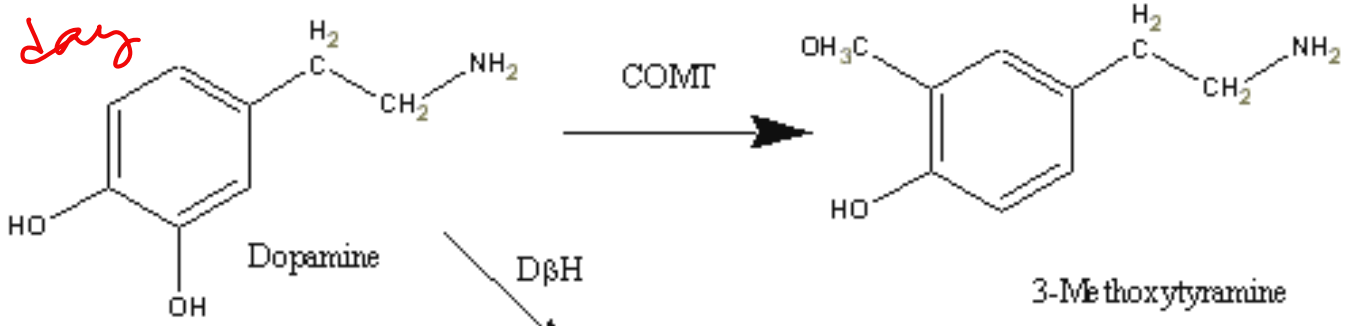
3-O-Methyldopa

Only about 1% gets to brain

AAD

Aromatic Amino Acid Decarboxylase ← you have this throughout your tissues

requires 4-8 g/day



Dopamine

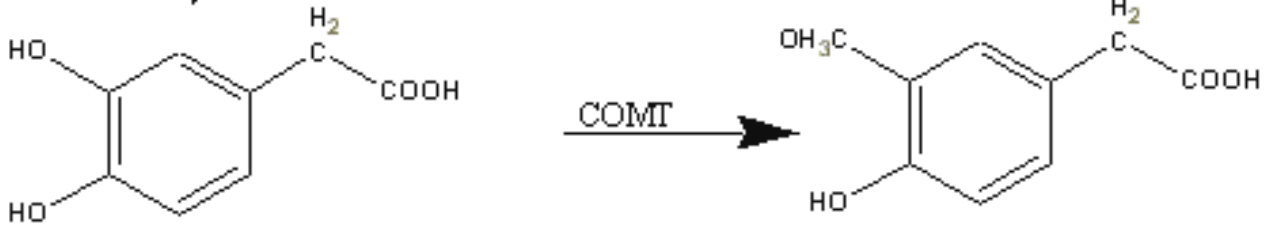
DβH

Norepinephrine

3-Methoxytyramine

MAO AD

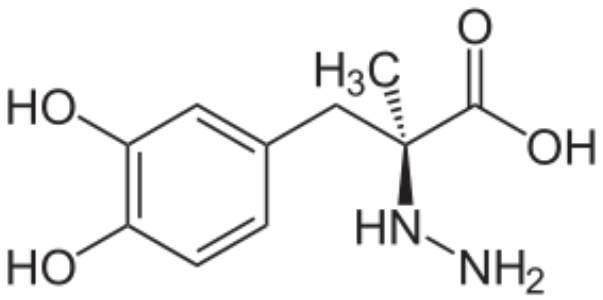
MAO AD



3,4-dihydroxyphenyl-acetic acid (DOPAC)

3-methoxy-4-hydroxy-phenylacetic acid (HVA)

Carbidopa → inhibitor for AAD



by adding this the dose ↓ 1g/day

Sentry Drug: a second drug that guards the principal drug, typically an enzyme inhibitor

Sentry Drugs: Examples

Carbidopa and Levodopa

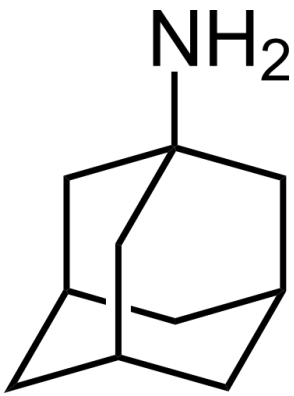
Adrenaline and Procaine

Clavulanic acid and Ampicillin

Parkinson's Treatments : Early

use indirect DA agonist

increase release of DA or enhance its action



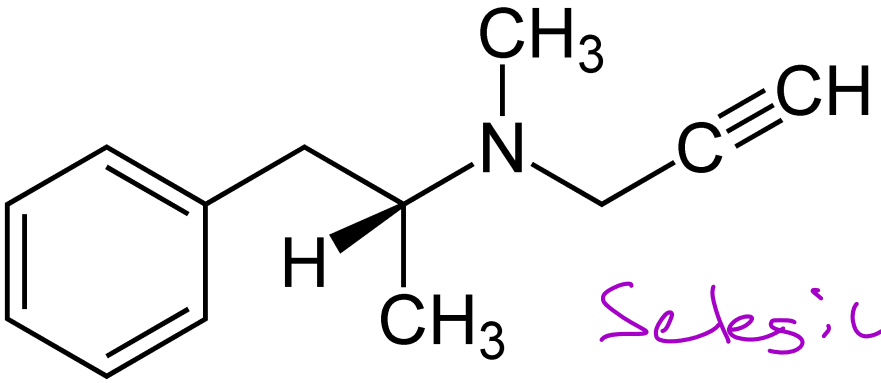
Amantidine

originally developed to treat/prevent flue

- DA reuptake inhibitor
- Stimulates release of DA

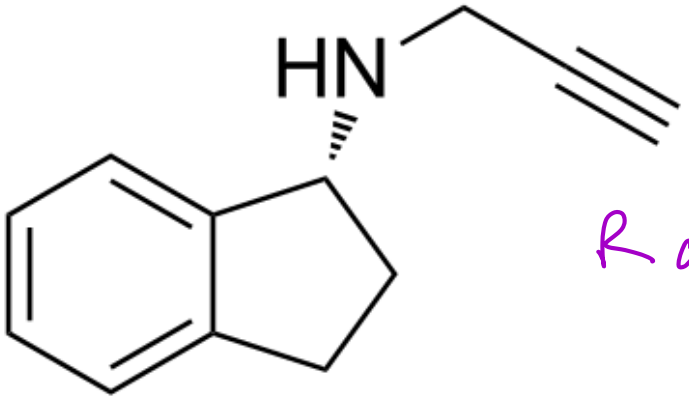
tolerance develops 6-8 months

Slow down metabolism of DA with MAOI's



Selegiline

might slow PD progression



Rasagaline

the ratio is important not just absolute values

Ach / DA balance

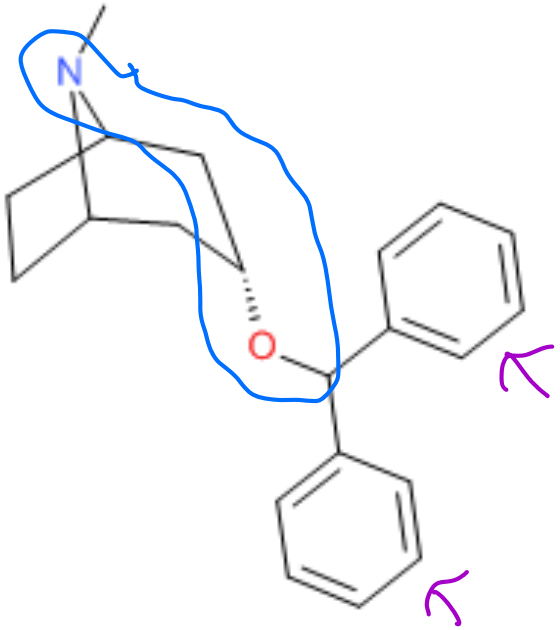
Ach antagonists were some of earliest treatments

Anticholinergics

need Balance of DA (inhibitory) ↙ increase this or

Ach (excitatory) ↙ decrease

Benztropine (Cogentin)



- Anticholinergic
- DA reuptake inhibitor

Dopamine Replacement Therapy

Phase 2 Therapy

Levodopa + Carbidopa

Side effects

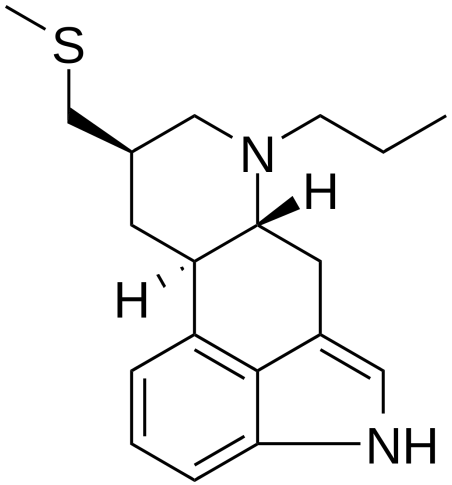
dyskinesias

Psychosis

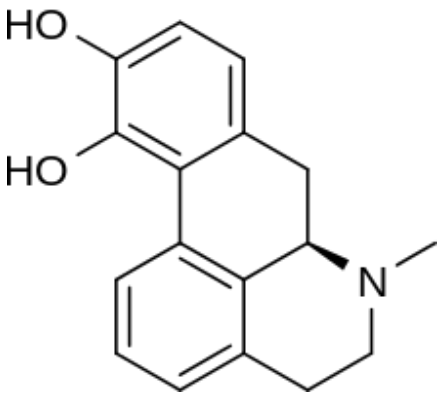
vomiting

Parkinsons : Late Stage

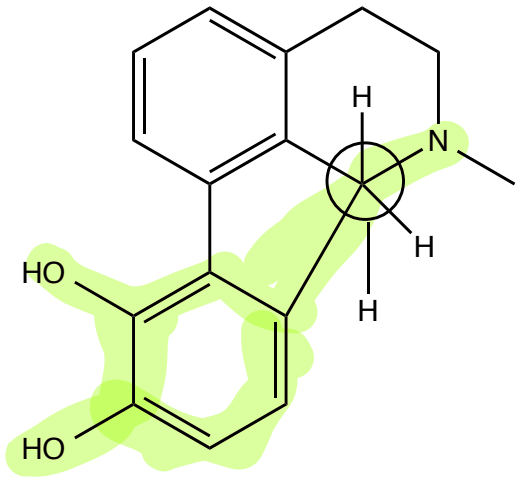
Phase 3 DA agonists

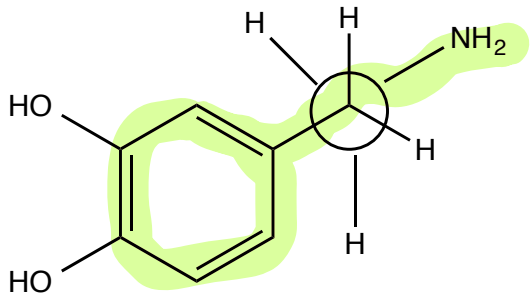


Pergolide

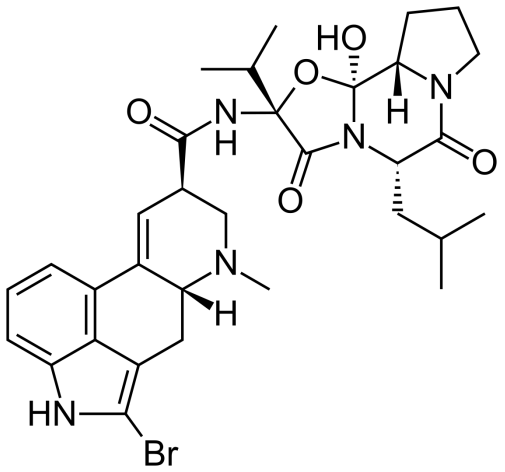


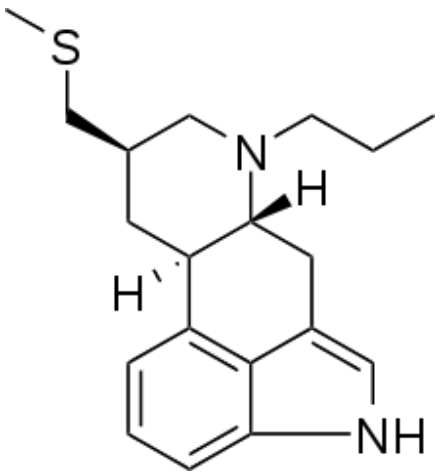
Apomorphine


H
N
H
H
HO
HO

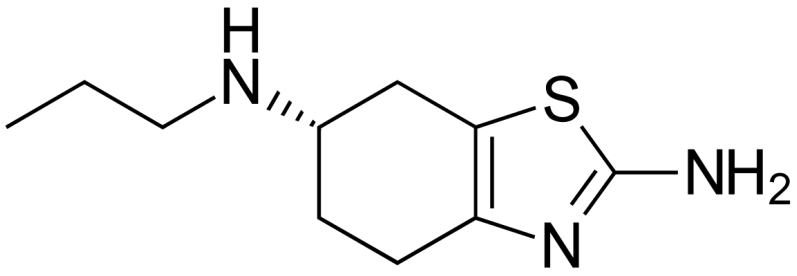

H
H
NH2
HO
H
HO
H

Dopamine Agonists





PD Depression Treatment

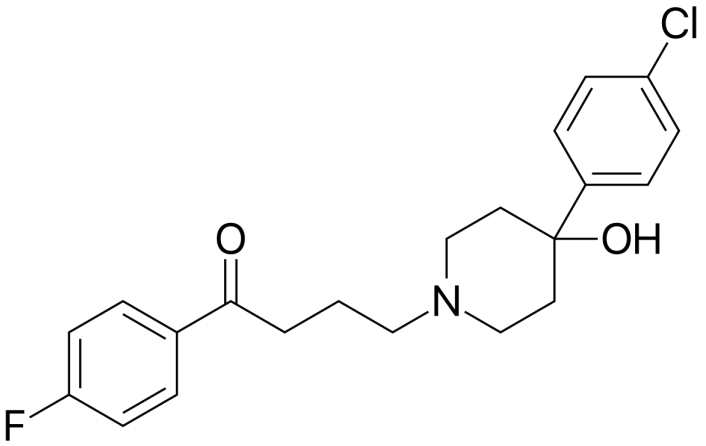


Protective Factors

Estrogen

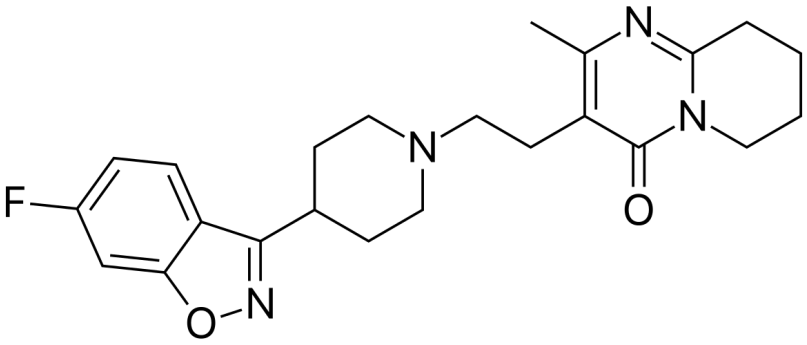
Caffeine

Dopamine Receptor Antagonists



Haloperidol

- potent antipsychotic
- DA_2 antagonist
- used for schizophrenia + Tourettes



Risperidone

- antipsychotic
- antidepressant

Huntington's Disease ← treat with DA antagonists

↑

excessive movement

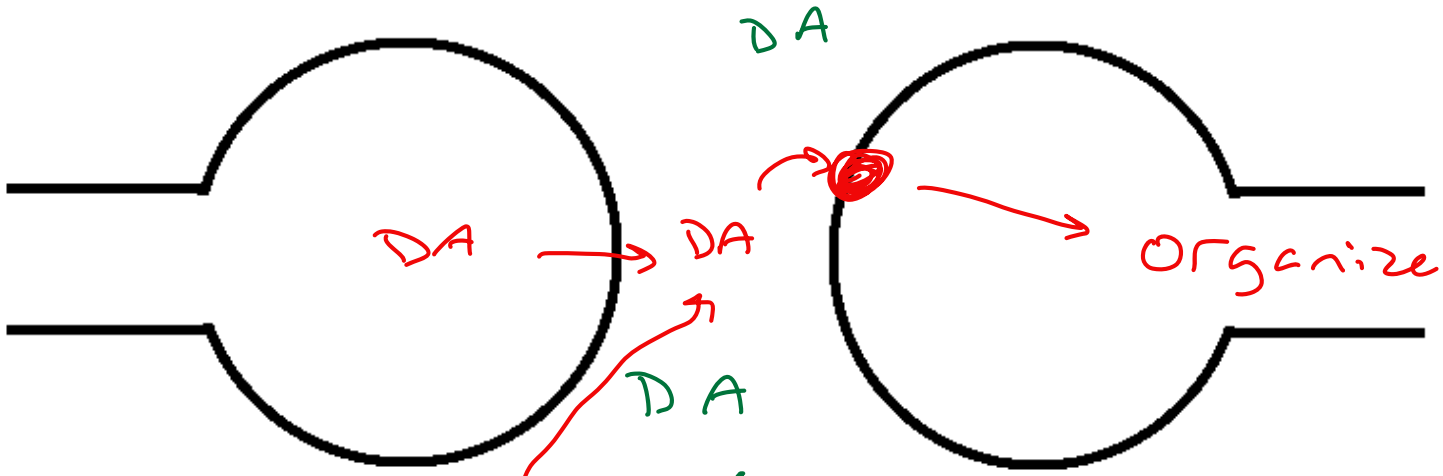
personality disorders

psychosis dementia

ADHD

Attention Deficit associated with low DA levels

3 Subtypes

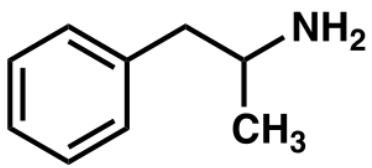


Tonic pool: DA present before signal

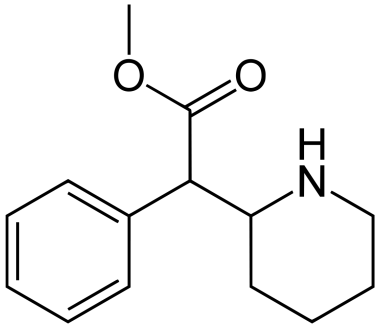
Phasic pool: DA from signal

If [DA] in tonic pool is too low adding the phasic pool isn't enough to get a high enough [DA] to get signal

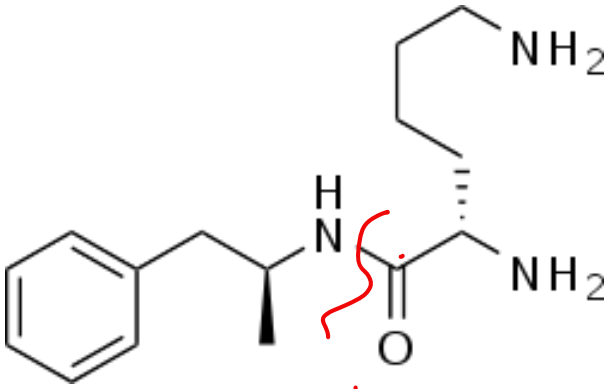
Stimulants for ADHD



Amphetamine (Adderall)
- Induces release of DA + NE
- Blocks DA reuptake
- Blocks NE reuptake
- Inhibits MAO



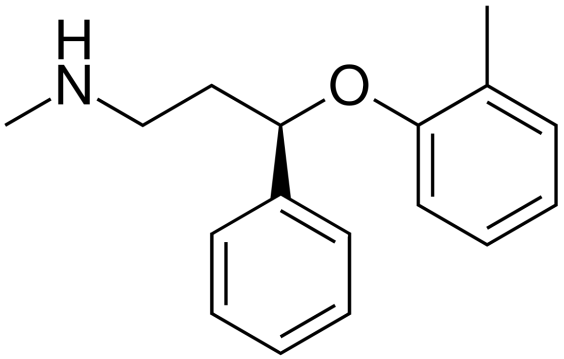
Ritalin (methylphenidate) more selective for DA



Vivanse
pro drug

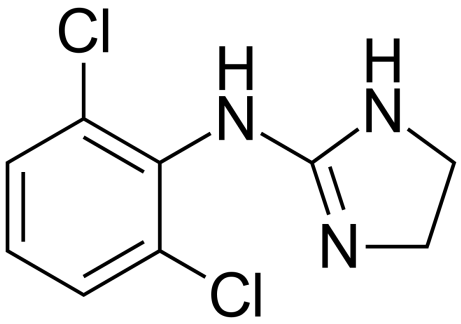
cleave here

Non Stimulants



Strattera

NET inhibitor



Clonidine

D_3 Receptor Antagonists

- May be useful for schizophrenic

- Treating addiction