

# Parkinson's & Hallucinogens

*Psilocybe mexicana*  
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Diseases of the Brain | Progressive conditions affect the body and mind in different ways

### Alzheimer's symptoms

**Cognitive:** Memory loss and deterioration in thinking and planning functions.

**Physical:** In mid-stage, disease could include slowness, rigidity and tremors.

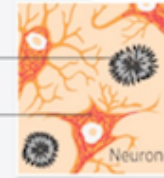
### INSIDE THE BRAIN

The cortex, particularly the **hippocampus**, key to memory, shrinks.

**Ventricles** (fluid-filled spaces within the brain) enlarge.

**Plaques** (amyloid deposits) cluster between neurons.

**Tangles** (twisted proteins) are found within neurons.



### Parkinson's symptoms

**Cognitive:** Loss of executive functions, including decision-making and controlling emotions.

**Physical:** Tremors, stiffness and slowed movements.

### INSIDE THE BRAIN

Cells shrink in the **substantia nigra**, where dopamine is produced.

**Lewy bodies** (clusters of alpha-synuclein protein) accumulate inside neurons.



Sources: Alzheimer's Association, Parkinson's Disease Foundation and helpguide.org

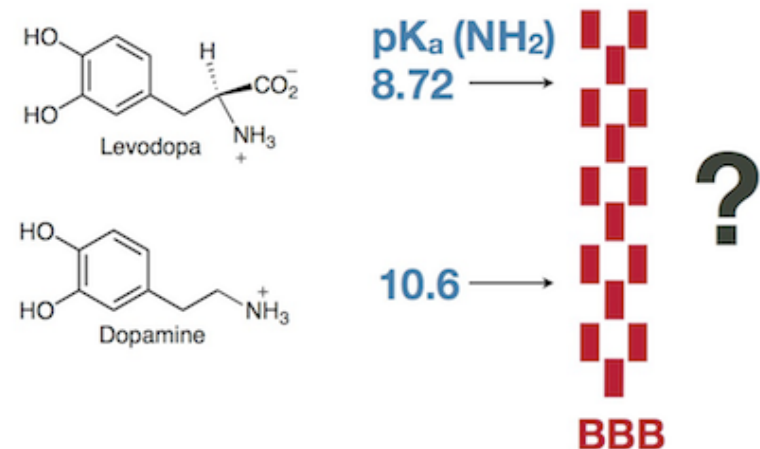
## Treatments for Parkinson's Disease

1. L-Dopa
2. Dopamine Releaser & Reuptake Inhibitors
3. MAO Inhibitors
4. Dopamine receptor agonists/stimulants

## Dopamine Replacements

### Why use L-Dopa, not Dopamine?

What are the different ionization states of L-Dopa?

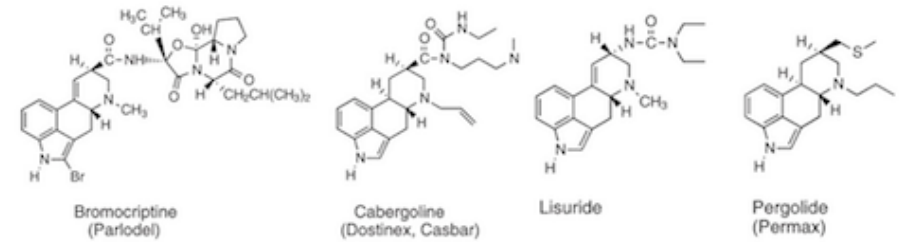
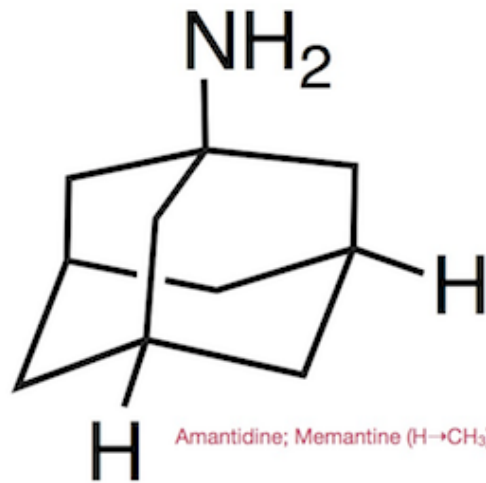


## 2. Dopamine Releaser & Reuptake Inhibitors

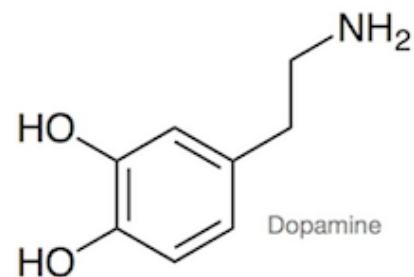
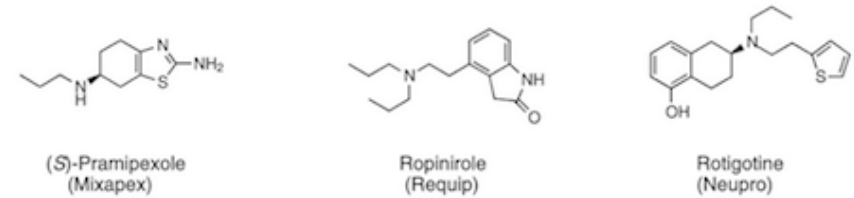
Exhibits antiparkinsonian effects during initial stage of disease.

pKa 10.8; protonated at physiological pH

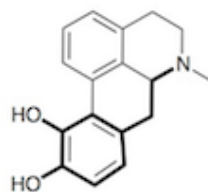
Cage-like structure may:  
1. be more lipophilic  
2. unlikely to get oxidised;  
found unchanged in urine



## 4. Dopamine receptor agonists/stimulants



## 4. Dopamine receptor agonists/stimulants



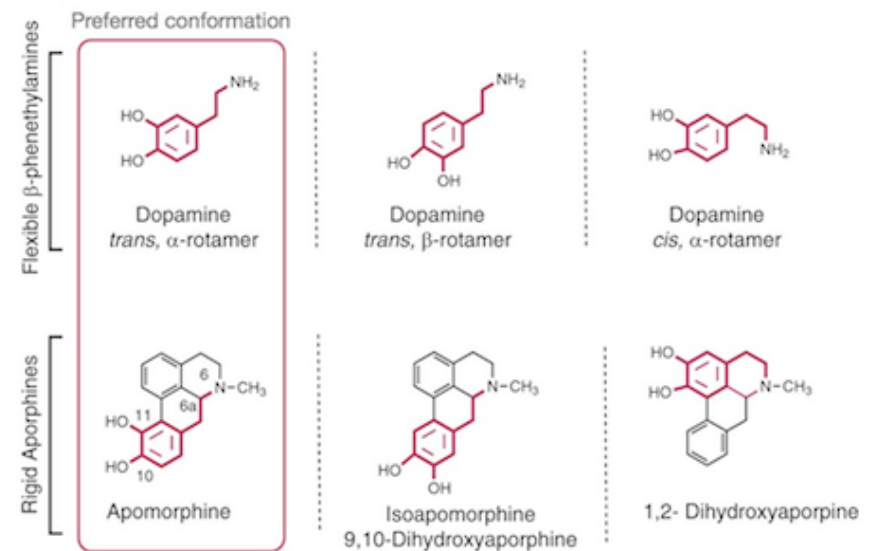
No validated models of D<sub>1</sub>- or D<sub>2</sub>-type receptors

Have to rely on QSAR, and probe molecules

Conformational information of Dopamine??

Flexible side-chain...

Thus, apomorphine is useful to study the SAR



Agonist for D<sub>1</sub>- or D<sub>2</sub>-type receptors

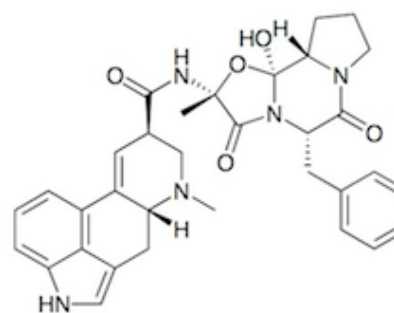
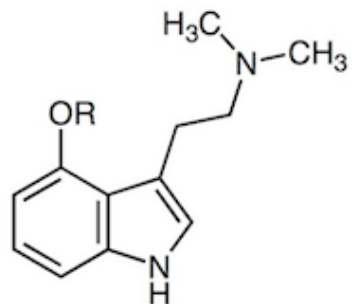
pKa 9 - able to cross BBB.

Limited clinical use - potent central emetic action



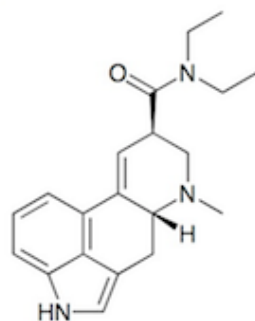
Psilocin  
R=H

Psilocybin  
R=PO<sub>3</sub>H<sub>2</sub>



medicinal uses of ergot alkaloids

ergotamine



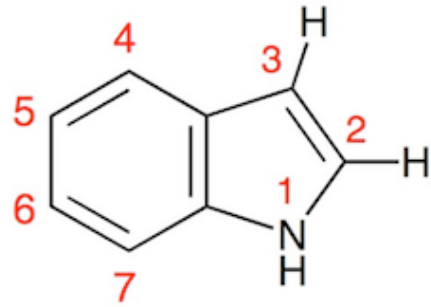
designed as circulatory  
and respiratory stimulant

LSD failed this test.

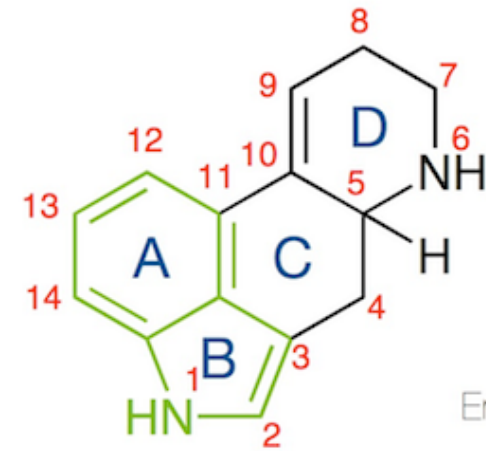
later, re-synthesised;  
wonderful experiences

lysergic acid diethylamide (LSD-25)

## The Chemistry LSD & THC

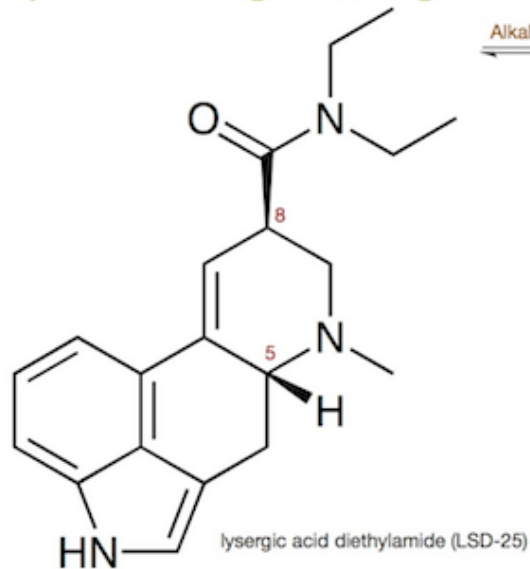


Where's the highest electron density?  
Which position is the most reactive,  
which is least?

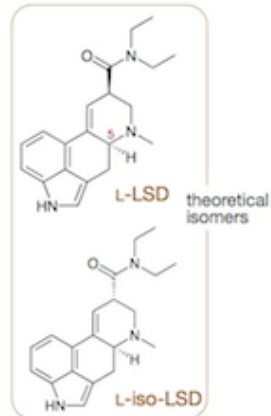
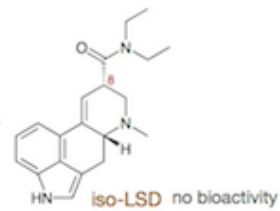


Ergoline nucleus

(+)-D-LSD [5*R*,8*R*]

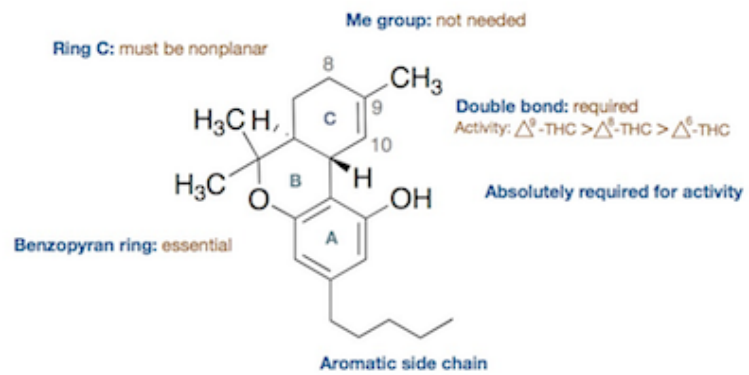
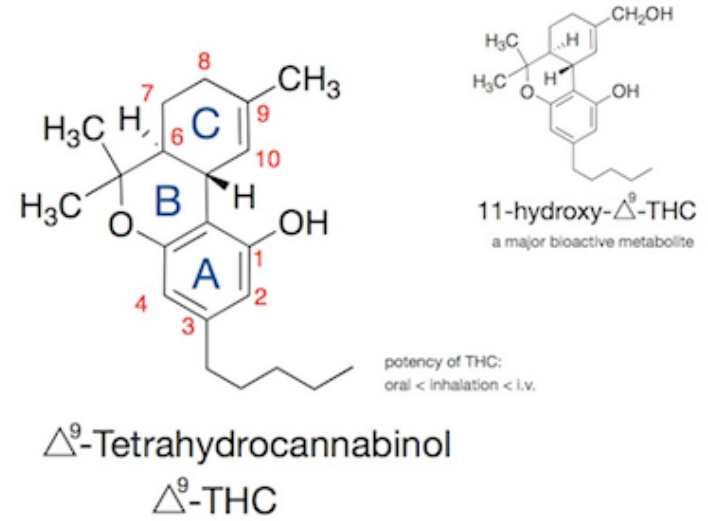


Alkali



*sativa, indica & ruderalis*  
Cannabis  
~ marijuana





### SAR of THC