

## CNS pharmacology part4

### **Drugs Used in Schizophrenia and Parkinson Disease**

Before we start:

Remember that both of these diseases are caused by imbalance in the dopaminergic system of the brain, so a drug that treats schizophrenia might cause side effects that look like Parkinson and vice versa.

**Schizophrenia** symptoms are of two types:

- Positive symptoms: hallucinations, delusions, disorganized thoughts, etc
- Negative symptoms: social withdrawal, flat affect, poverty of speech, etc

There are two theories trying to explain this disease

- Dopamine theory: schizophrenia arises because of excessive dopamine in the brain. This excessive dopamine is occupying *D2 receptors*
- Serotonin theory: Serotonin also plays a role in the etiology of schizophrenia

## ANTIPSYCHOTICS

Note: it takes you 4 to 6 weeks of treatment with an antipsychotic to see maximal response.

### 1. Typical antipsychotics

- Drugs: **Haloperidol**, chlorpromazine
- Mechanism: blockade of D<sub>2</sub> receptors
- Useful in treating positive symptoms of schizophrenia but not the negative symptoms
- Side effects **from dopamine blockade**:
  - Extrapyrimalidal symptoms (EPS): which are involuntary movements usually begin in the mouth.
    - Acutely:
      - Acute dystonia** (sustained muscle contractions after 1 to 5 days of usage),
      - Akathesia**; need to be in constant motion مثل أم العروس (after 5 to 6 days),
      - Parkinsonism** (after 5 to 30 days)
        - These side effects are caused by ↓dopamine
        - Management: give an antiparkinsonian agent that is an *antimuscarinic* agent.
    - Chronically (after months to years of therapy):
      - Tardive dyskinesia**; an oral-facial dyskinesia
        - This side effect is caused by *excess* dopamine (long-term dopamine antagonism results in upregulation of dopamine receptors)
  - Side effects from *alpha blockade* (orthostatic hypotension) and *histamine blockade* (sedation) are also present. Tolerance to the sedative effect of the drug does develop though.

Think of it that way:

- Typical theory: It's dopamine fault! → *Typical antipsychotics* block dopamine
- Atypical theory: It's serotonin's as well!! → *Atypical antipsychotics* block serotonin.

## 2. Atypical antipsychotics:

- Drugs: risep~~eridone~~, ziprasid~~one~~ clozapine, olanzapine,
- Queti~~apine~~, sulpiride, aripiprazole.
- Mechanism: blockade of D<sub>2</sub> (less than typical) and 5-HT<sub>2</sub> receptors
- Useful in treating *BOTH positive and negative* symptoms of schizophrenia (more effect on the positive symptoms though)
- Less likely to produce EPS (because of their lower selectivity to dopamine receptors)
- Side effects from *alpha blockade* (orthostatic hypotension) and *histamine blockade* (sedation) are also present

### Risperidone

- *dopamine blockade* results in
  - EPS at high doses. Anticholinergic drugs are prescribed with riseriperidone to avoid developing these side effects
  - Release of tonic inhibition of prolactin secretion by dopamine → ↑ prolactin → galactorrhea and amenorrhea in females, gynecomastia and impotence in males.

### Clozapine and Olanzapine

- **Least likely to produce EPS**
- Significant **weight gain**, hyperglycemia (diabetogenic) and hyperlipidemia
- **Clozapine: Agranulocytosis** is a potentially fatal side effect (requires weekly WBC count)

Likelihood to develop EPS:

Haloperidol > other typical > atypical > clozapine and olanzapine.

## Quetiapine

- *Anticholinergic* side effects: dry mouth, constipation, etc
- *Less* weight gain than clozapine and olanzepine
- Does *NOT* elevate prolactin

\*If any of the aforementioned atypical antipsychotics was prescribed, it shouldn't be stopped before 3 months of treatment

## Aripiprazole

- D<sub>2</sub> receptor **partial** agonist  
(partial = less potent side effects)
- Cause dizziness (avoid in the elderly)

*Flashback:*

Serotonin Antagonists Reuptake Inhibitors (SARIs) also cause dizziness and should be avoided in the elderly

\*\*Abrupt discontinuation of antipsychotics results in withdrawal symptoms

## Parkinson Disease:

degeneration of dopaminergic neurons with imbalance between dopamine and acetylcholine

(↓DA and ↑Ach)

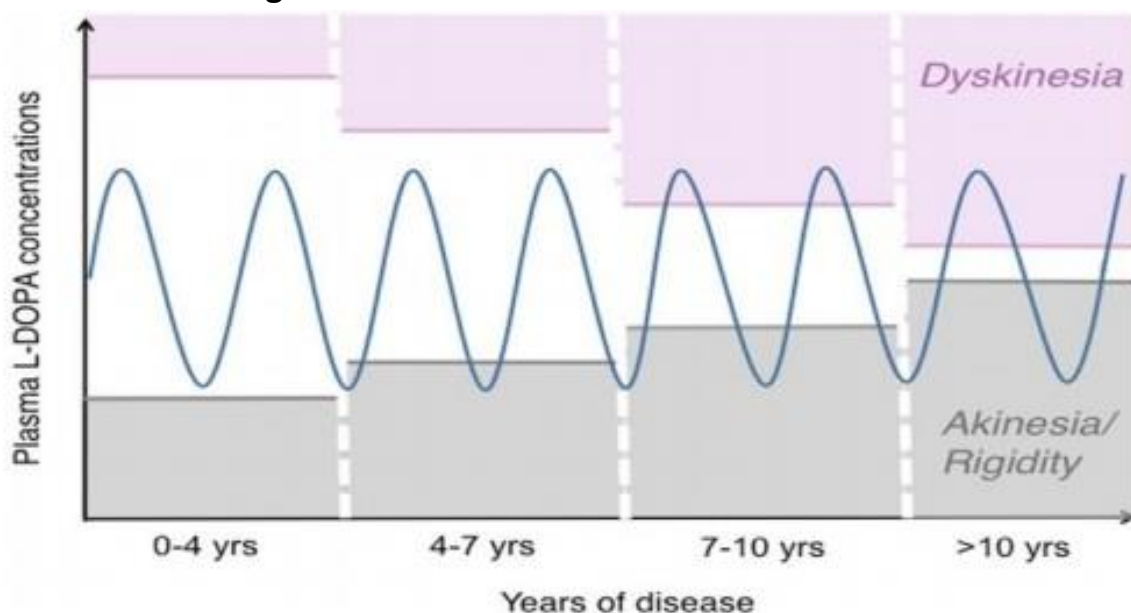
Pharmacologic strategy: restoration of dopamine and antagonizing acetylcholine activity.

Drugs used:

### Levodopa

- Gets converted to dopamine
- Given with **Carbidopa**
  - **Carbidopa** is a dopamine *decarboxylase inhibitor* that blocks peripheral conversion of levodopa to dopamine so more of it reaches the CNS
- Side effects:
  - *Motor control fluctuation* (on-off effect)  
this happens with progression of the disease and need to give higher doses of the drug. When you administer the drug (peak) there will be too much dopamine → **Dyskinesia** (sporadic movements).  
When the concentration decreases (trough) the patient will have Parkinson symptoms again (Akinesia/ rigidity)-

### **Wearing off**



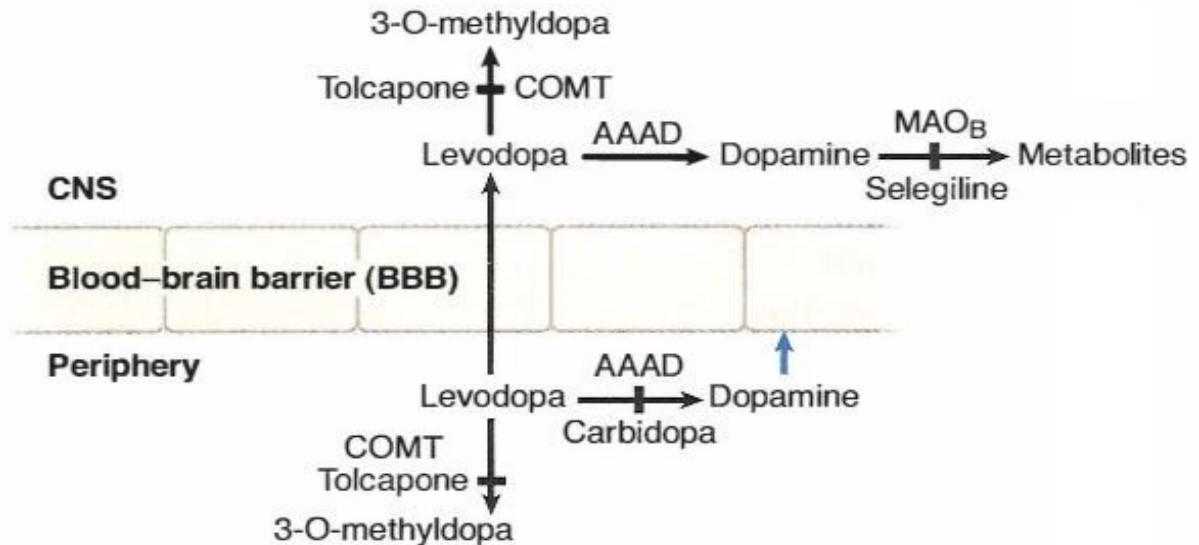
- Vomiting (dopamine stimulates the antiemetic center)
- Cardiac side effects (tachycardia, extrasystole)
- Hallucinations, dyskinesia, schizophrenic attacks

### Selegiline

- MAO<sub>B</sub>- **selective** inhibitor (no tyramine interactions *because it is given in low doses*)
- Little benefit as monotherapy. Used as an adjunct to levedopa.

### Tolcapone and Entacapone

- Catechol-O-methyltransferase (COMT) converts levodopa to a nonactive metabolite
- Tolcapone and Entacapone inhibit COMT and enhance levodopa effects
- **Tolcapone** is hepatotoxic



### Dopamine receptor ( D<sub>2</sub>) agonists:

#### Bromocriptine, Pramipexol and **Ropinirole**

- Less likely to produce dyskinesia and motor fluctuations (because of longer half life)
- More likely to produce nausea, hallucination and hypotension

#### **Amantidine**

- Antiviral, *block cholinergic receptors and ↑dopamine release* (بيضرب عصفورين بحجر) and block some NMDA glutamate receptors
- Side effects: CNS symptoms (restlessness, agitation, dizziness, etc)
- Mild action. Not really used.

### Drugs decreasing Ach functions

#### **Benzotropine, Biperidine and Atropine**

- Side effects:
  - Atropine-like ( papillary dilation, constipation, etc)
    - **Contraindicated in glaucoma**
  - May cause mood change
- Remember; *the drug of choice for treating a schizophrenic patient from Parkinson-like side effects is antimuscarinic drugs*

Extra note: mydriasis obstructs the outflow of aqueous humor through the canal of Schlemm

والصلاة والسلام على أكرم المرسلين

شكر خاص لسندس الخطيب و نيفين عزام اللتين كتبتا الشيتات ولولا ذلك لما أمكن كتابة هذا الملخص