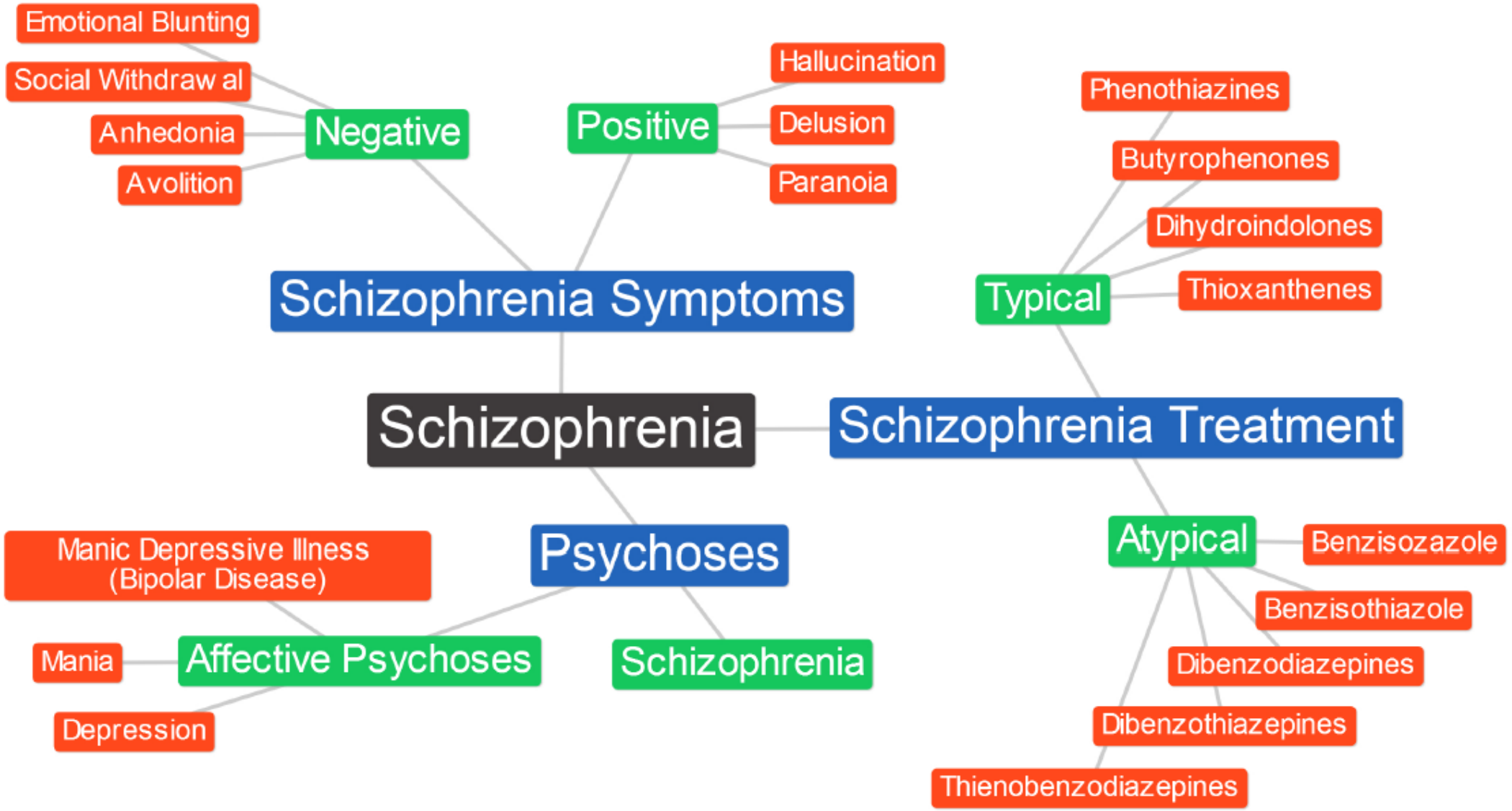
Lecture 10

Drugs used in schizophrenia

Objectives:

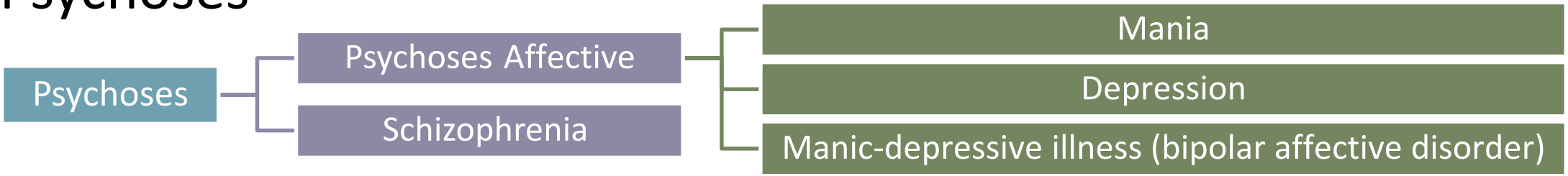
- List the classification of antipsychotic drugs used in schizophrenia.
- Describe briefly the mechanism of antipsychotic action of these drugs.
- Describe the pharmacological actions of antipsychotic drugs.
- Relate between pharmacological actions & adverse effects of antipsychotic drugs.
- Enumerate the clinical uses of antipsychotic drugs.
- Describe the advantages of atypical antipsychotic drugs over typical drugs.

- Additional Notes
- Important


Emotional Blunting
Social Withdraw al
Anhedonia
Avolition
Negative
Positive
Hallucination
Delusion
Paranoia
Schizophrenia Symptoms
Phenothiazines
Butyrophenones
Dihydroindolones
Thioxanthenes
Typical
Schizophrenia
Schizophrenia Treatment
Manic Depressive Illness
(Bipolar Disease)
Psychoses
Atypical
Benzisozazole
Benzisothiazole
Dibenzodiazepines
Dibenzothiazepines
Thienobenzodiazepines
Mania
Affective Psychoses
Schizophrenia
Depression

Mind Map

Psychoses



Schizophrenia

Definition : It is a thought disorder characterized by divorcement from reality in mind of patient.

- it may involve hallucinations, delusions , intense suspicion , felling of persecution or control by external forces (paranoia).

Positive symptoms : 1- hallucinations 2- Delusions 3- paranoia

Negative symptoms : 1- Social withdrawal 2- Anhedonia (absence of pleasure) 3- Emotional blunting

Dopamine System and Receptors

Dopaminergic pathways in the brain :

1- Mesolimbic - mesocortical pathway (behavior)
2- Nigrostriatal pathway (co-ordination of voluntary movements)
3- Tuberoinfundibular pathway (endocrine effects)
4- Medullary - periventricular pathway (metabolic effects)

- There are at least five subtypes of Dopamine receptors: D1,D2,D3,D4,D5

Classification of Antipsychotic drugs (According to chemical structure)

Typical Antipsychotic Drugs	
Phenothiazine derivatives	Thioridazine
Butyrophenones	Haloperidol
Thioxanthene	Thiothixene
Atypical Antipsychotic Drugs	
Dibenzodiazepines	Clozapine
Benzisoxazoles	Risperidone
Thienobenzodiazepines	Olanzapine
Dibenzothiazepines	Quetiapine
Benzisothiazoles	Ziprasidone

Typical & Atypical Antipsychotic Drugs

Pharmacological Actions			Mechanism
CNS	1) Antipsychotic effect.	• Produce emotional quieting & psychomotor. • Decrease hallucination & delusion & agitation.	Block Dopamine (DA) receptors in the mesolimbic system.
	2) Extrapyramidal symptoms.	• Abnormal involuntary movement (Tremor & Parkinsonism & Tardive dyskinesia [irreversible neurological disorder of involuntary movements caused by long-term use of antipsychotic drugs]).	Block Dopamine receptors in the nigrostraiatum.
	3) Endocrine effect	• Galactorrhea. (secretion of breast milk in women who are not breastfeeding an infant). • Amenorrhea. (absence of menstrual periods). • Gynecomastia (excess growth of the adipose tissue in a male breast). • Impotence.	Prevent Dopamine inhibition of prolactin release → from pituitary → hyperprolactinemia.
	4) Metabolic effect	• Change in eating behavior & weight gain.	Block Dopamine receptors in the medullary-perventricular pathway.
	5) Antiemetic effect	• Against drugs or disease Induce vomiting (not motion sickness)	Block Dopamine receptors in the CTZ (chemical trigger zone) of the medulla
ANS	1) Anticholinergic	Blurred vision, Dry mouth, Urinary retention, Constipation.	Block muscarinic receptors
	2) Antiadrenergic	Postural hypotension, Impotence, Failure of ejaculation.	Block alpha (a) – adrenergic receptors
Other	1) Temperature regulation.	• May cause lowering of body temperature.	Heat loss as a result of vasodilation (a-blockage) or Due to central effect.
	2) ECG changes	• Prolongation of QT interval • Abnormal configuration of ST- segment & T wave.	_____
	3) Antihistaminic	• Sedation due to H1 receptors blockage.	
	4) Quinidine like	_____	_____

Typical & Atypical Antipsychotic Drugs

Side Effect			Drug
C.N.S	Sedation, Downiness, Fatigue		Haloperidol, Riseperidone.
	Extrapyramidal symptoms.	• Occurring Early in treatment: Parkinson's syndrome. • Occurring Late in treatment: Tardive Dyskinesia[1], Neuroleptic malignant syndrome[2].	
	1. Involuntary movements of lips, tongue, face, jaws ,Choreoathetosis : combination of chorea (irregular migrating contractions) and athetosis (twisting). 2. Rare but life threatening. Symptoms are muscle rigidity and high fever (clinically similar to anaesthetic malignant hyperthermia). Leukocytosis and high fever associated with this syndrome may wrongly suggest an infection.		
	Endocrine effect.	Gynecomatia, Galactorrhea, Amenorrhea.	
A.N.S	Anticholinergic effect.	Blurred vision, Dry mouth, Urinary retention, Constipation.	Chlorpromazine, Clozapine.
	Antiadrenergic effect.	Postural hypotension, Impotence, Failure of ejaculation.	Chlorpromazine, Thioridazine.
Other	Miscellaneous effect	Obstructive jaundice, Granular deposits in cornea, Retinal deposits, Weight gain.	Thioridazine (retinal deposits)
	Agranulocytosis (↑ vulnerability to infection)	Happen after 6-18 weeks Must take WBC weekly.	Clozapine (1-2%)
	Seizure		Clozapine

Therapeutic Uses

Psychiatric	Non-psychiatric
1) Schizophrenia. (primary indication) 2) Acute mania. 3) Manic-depressive illness (bipolar affective disorder) → give him during manic phase.	1) Nausea & vomiting. (Prochlorperazine & Benzquinamide only use for antiemetic) 2) Pruritis. 3) Preoperative sedation (rare use)

Pharmacokinetics	Incompletely absorbed, Highly lipid soluble, Highly bound to plasma proteins, Undergo extensive first-pass hepatic metabolism, Excretion by the kidney

Atypical Antipsychotic Drugs (first line treatments)

Drugs	Benzisothiazoles Ziprasidone	Dibenzodiazepines Clozapine	Benzisoxazoles Risperidone	Thienobenzodiazepines Olanzapine	Dibenzothiazepines Quetiapine
R	Blocks D_2 & 5HT2	Blocks both D_4 & $5HT_2$	Blocks D_2 & $5HT_2$	-Blocks D_1- D_4 & $5HT_2$	Blocks D_1-D_2 & $5HT_2$
ADES	• Drowsiness • Akathisia • Headache • Dizziness • Weight gain ○ Warning: Increase mortality in elderly patients with dementia-related psychosis.	• Agranulocytosis • Seizures • Myocarditis • Excessive salivation (during sleep)	• Postural hypotension. • QT prolongation. • Weight gain. ○ Contraindicated in patients with long QT interval	• Weight gain • Sedation • Flatulence , increased salivation & thirst • Postural hypotension	• Sedation Hypotension • Sluggishness • Dry mouth • Increased appetite (weight gain) • Abdominal pain • Constipation
Notes	1/no extrapyramidal side effects. 2/Effective in treatment of resistant schizophrenia. 3/Are effective on both positive & negative symptoms. 4/Block both dopaminergic & serotonergic receptors.				
Uses	Refractory cases of schizophrenia and To reduce the risk of recurrent suicidal behavior in patients with schizophrenia .				
D.I	• should not be used with any drug that prolongs the QT interval • Activity decreased by Carbamazepine (inducer of CYP3A4) • Activity increased by Ketoconazole (inhibitor of CYP3A4)	————————			

Sammary

Drug	ADR	Pharmacological Action	Indications
Clozapine Blocks both D_4 & $5HT_2$ receptors	Agranulocytosis, Seizures, Myocarditis, Excessive salivation (during sleep)	On CNS:- • Anti-psychotic effects • Extrapyramidal Symptoms • Endocrine effects • Metabolic effects • Anti-emetic effects On ANS:- • Anti-cholinergic effects • Anti-adrenergic effects Other actions: • Tempreture regulation • ECG changes • Antihistamine effects • Quinidine like actions	• Refractory cases of schizophrenia. • Reduce the risk of recurrent suicidal behavior in patients with schizophrenia
Risperidone Blocks D_2 & $5HT_2$ receptors	Postural hypotension, QT prolongation, Weight gain		
Olanzapin Blocks D_1- D_4 & $5HT_2$ receptors	Weight gain, Sedation, Flatulence , increased salivation & thirst, Postural hypotension		
Quetiapin Blocks D_1-D_2 & $5HT_2$ receptors	Sedation, Hypotension, Sluggishness, Dry mouth		
Ziprasidone Blocks D_2 & $5HT_2$ receptors	Drowsiness, Akathisia, Headache, Dizziness, Weight gain		

1. **which one of the following is positive symptom?**
   A. Anhedonia.
   B. Social withdrawal.
   C. Emotional blunting.
   D. Paranoia.

2. **Which one of the following of the drug can cause seizure and agranulocytosis ?**
   A. Ziprasidone
   B. Risperidone
   C. Clozapine
   D. thioridazine

3. **All the following drugs are Block D2 except?**
   A. Ziprasidone
   B. Olanzapine
   C. Risperidone
   D. Quetiapine

4. **Atypical drugs exert their antipsychotic action through blocking?**
   A. Dopamine receptors
   B. Serotonin and dopamine receptors
   C. Dopamine and adrenalin receptors.
   D. Serotonin receptors

5. **A patient comes in cardiology clinic. With routinely investigation in ECG, the cardiologist suspects the patient has hypercalcemia, but in History, the patient take medication that shows wrong diagnosis. What is the drug?**
   A. Chlopromazine
   B. Clozapine
   C. Olanzapine
   D. Risperidone

Answers: 1. D 2. C 3. B 4. B 5. D

MCQS FROM 433

A patient with Schizophrenia, he took medication. Some times, he feels headache, and drowsing & he can't sit.

1. What is the drug he took?
   - Ziprasidone

2. Which receptors blocked by this drug?
   - D2 & 5HT2 receptors

3. Give one example of drug-drug interaction that can happen as a result of the drug he took & explain the mechanism?
   - Carbamazepine
   - Decreased activity by induce CYP3A4

SAQs

Good luck!

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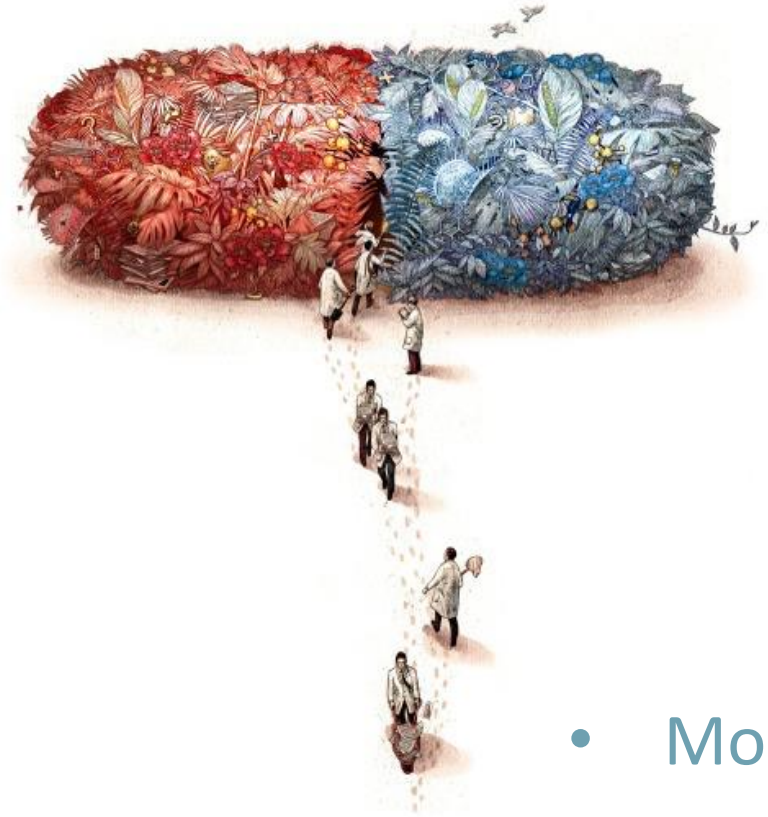

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