

# Antipsychotic drugs

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# To be covered in lecture..

- Brief Introduction about condition
- Dopamine, Serotonin and Glutamate hypothesis of schizophrenia
- Antipsychotics drugs classification
- Common ADRs
- Neurological side effects of antipsychotics
- Some individual drugs
- MCQs

# Psychosis

- Brief psychotic disorders
- Schizophreniform disorders
- Schizophrenia
- Delusional disorders
- Schizoaffective disorder

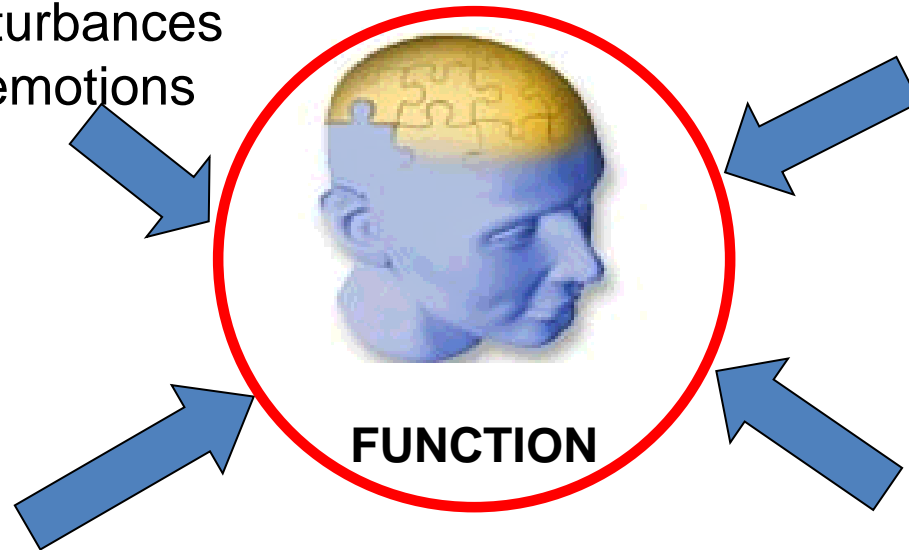
# Schizophrenia - symptoms

## Positive Symptoms(↑↑DA)

Hallucinations  
Delusions (bizarre, persecutory)  
Disorganized Thought  
Perception disturbances  
Inappropriate emotions

## Negative Symptoms(↓↓NMDA/↓DA)

Blunted emotions  
Anhedonia  
Lack of feeling



**FUNCTION**

## Cognition

New Learning  
Memory

## Mood Symptoms

Loss of motivation  
Social withdrawal  
Insight  
Demoralization  
Suicide

# Prognosis of Schizophrenia

- 10% continuous hospitalization
- $\leq 30\%$  recovery = symptom-free for 5 years
- 60% continued problems in living/episodic periods

# Etiology

- A gene encodes for **neuregulin-1 (NRG1 - ErbB4)** has been associated with schizophrenia.
- **Hereditary** Influences may account for 10% of schizophrenia cases
- **Prenatal/perinatal Biological Trauma** 10% cases of schizophrenia

Note- **NRG1** is a **pleiotropic growth factor**, important in nervous system development and functioning

# Schizophrenia Pathophysiology

## Schizophrenia Pathophysiology

## Pharmacologic Profile of APDs

**Past** Excess dopaminergic activity

Dopamine D<sub>2</sub>-receptor antagonists

### Present

-Renewed interest in the role of serotonin (5-HT)

Combined 5-HT<sub>2</sub>/D<sub>2</sub> antagonists

### Future

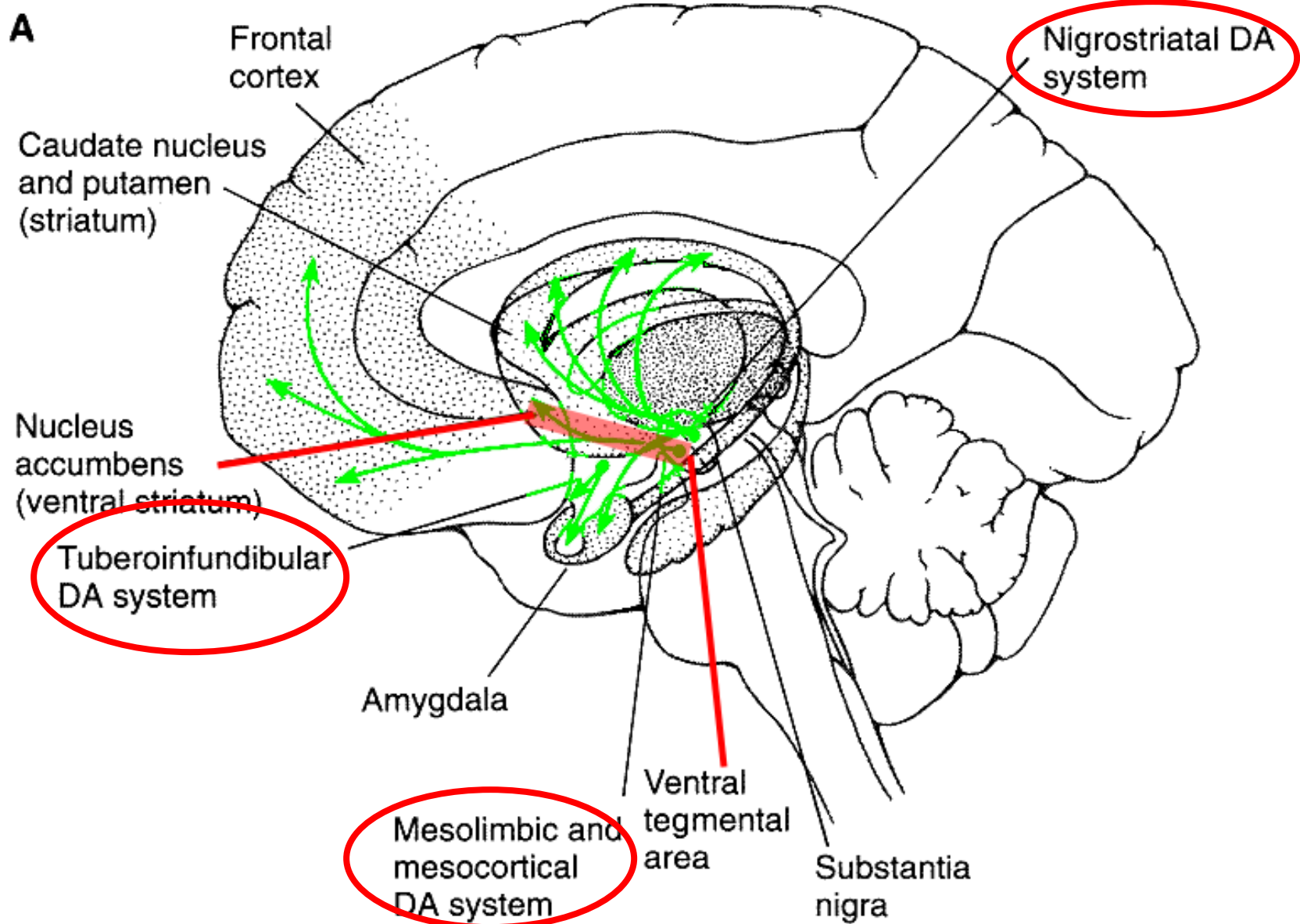
-NMDA

NMDA agonists (*glycine, d-serine*)

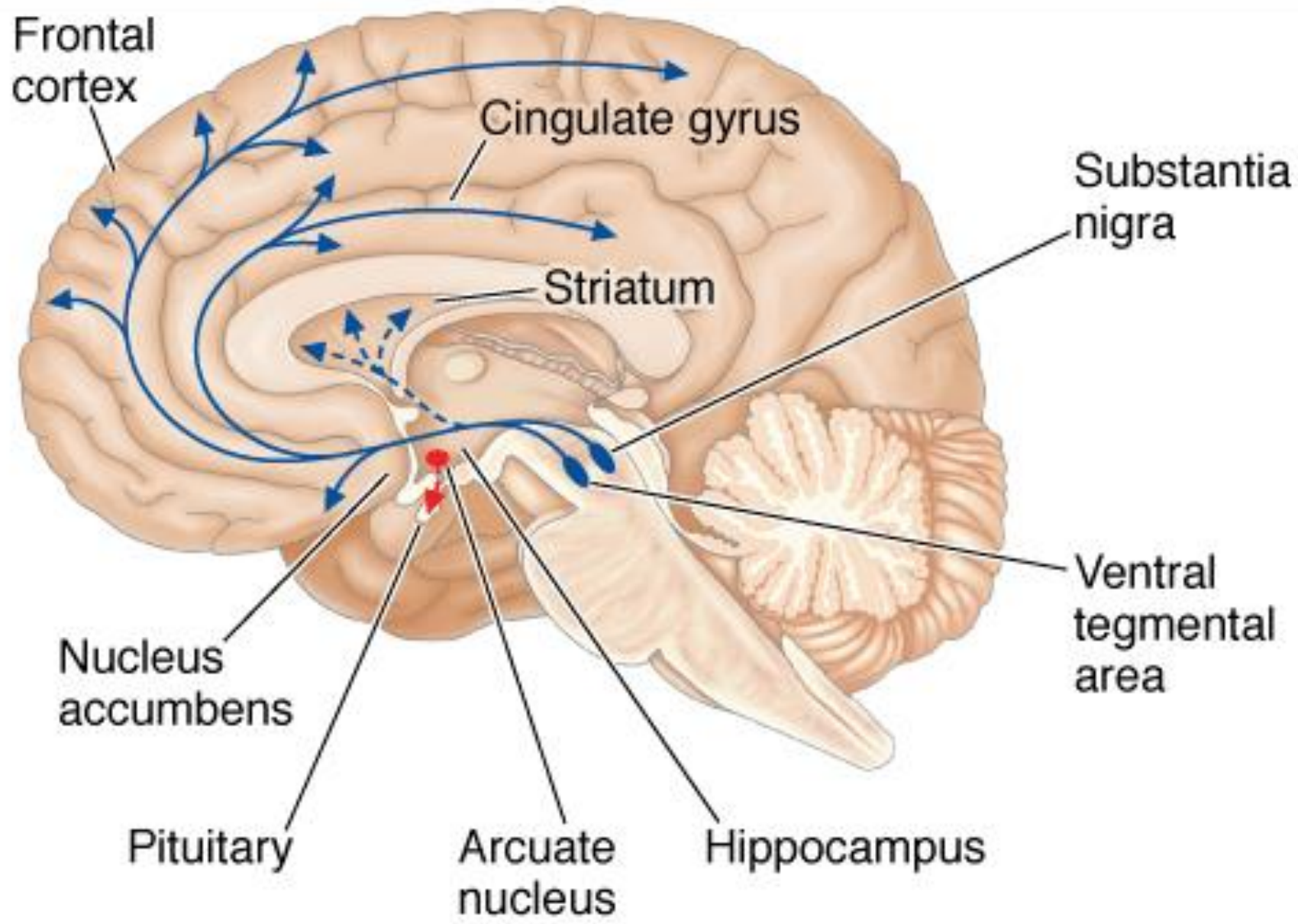
Imbalance in cortical communication and cortical-midbrain integration, involving multiple neurotransmitters

More selective antagonists  
Mixed agonist/antagonists  
Neuropeptide analogs

# Dopaminergic Pathways and Innervation







# Schizophrenia - Dopamine Hypothesis

- **Amphetamines and cocaine** (by enhancing central dopaminergic neurotransmission) can cause a psychosis that resembles the positive symptoms of schizophrenia.
- Low doses of amphetamine can induce a psychotic reaction in schizophrenics in remission.
- Postmortem tissue revealed increased numbers of DA receptors (in particular D2-like) in schizophrenic patients

# Schizophrenia-Serotonin Hypothesis

- Hallucinogens such as **LSD** (lysergic acid diethylamide) and **mescaline** are **serotonin** (5-HT) **agonists**
- 5-HT<sub>2A</sub>-receptor blockers relieve the condition (atypical antipsychotics-clozapine & quetiapine)
- 5-HT<sub>2A</sub>-receptor modulate the release of **dopamine** in the cortex, limbic region, and striatum

# Schizophrenia - **Glutamate Hypothesis**

- Psychotomimetic effects appear by **phencyclidine (PCP)** and **ketamine (NMDA-blockers)**
- **Hypofunction of NMDA receptors** is a contributory factor in the pathophysiology of schizophrenia
- The effects of **clozapine on negative symptoms and cognition** may be through **activation of the glycine modulatory site on the NMDA receptor.**

# Drugs

- **Phenothiazines**

- Aliphatic side chain:

- Chlorpromazine

- Triflupromazine

- Piperidine side chain:

- Thioridazine

- Piperazine side chain:

- Trifluoperazine

- Fluphenazine

- **Butyrophenones**

- Haloperidol

- Trifluoperidol

- Penfluridol

- **Thioxanthenes**

- Flupenthixol

- **Heterocyclics**

- Pimozide

- Loxapine

- Levosulpiride

- **Atypical antipsychotics**

- Clozapine

- Olanzapine

- Quetiapine

- Risperidone

- Iloperidone

- Paliperidone

- Ziprasidone

- Lurasidone

- Aripiprazole

- Asenapine

- Sertindole

- Zotepine

# ANTIPSYCHOTICS

- Older drugs (1<sup>st</sup> gen)
  - “Typical”, conventional, traditional neuroleptics, major tranquilizers
  - Modeled on D<sub>2</sub> antagonism
  - EPS
- Atypical drugs (2<sup>nd</sup> gen)
  - Modeled on 5-HT<sub>2</sub>/D<sub>2</sub>/D<sub>4</sub> antagonism
  - Less EPS, prolactin effects
  - Weight gain, sedation, diabetes

# Antipsychotics & receptors

Receptors blocked	Therapeutic effect	Adverse effects
D <sub>2</sub>	Improved +ve symptoms	EPS
	Antiemetic action	Hyperprolactinemia
D <sub>4</sub>	Improved -ve symptoms	Reduced EPS
5-HT <sub>2</sub>	Improved -ve symptoms	Reduced EPS
$\alpha_2$	Improved -ve symptoms	
$\alpha_1$		Postural hypotension
M		Anticholinergic S/E
H <sub>1</sub>		Sedation, weight gain



# Adverse Effects

- **Sedation** - initially considerable (tolerance after a few weeks)
- **Postural hypotension** -  $\alpha$ 1- blockade (**chlorpromazine**) tolerance can develop
- **Anticholinergic effects** - blurred vision, dry mouth, constipation, urinary retention (**thioridazine**)
- **Endocrine effects** - increased prolactin secretion can cause galactorhea; results from antidopamine effect
- **Hypersensitivity reactions** - jaundice, photosensitivity (**chlorpromazine**), agranulocytosis (**clozapine**)

**Weight gain** – 40% - weight gain now attributed to ratio of binding to D2 and 5-HT2 & H1 receptors

## **Sexual dysfunction**

- result from NE and SE blockade
- **erectile dysfunction** in 23-54% of men
- **retrograde ejaculation**
- **loss of libido**

## **Seizures**

## Sensitivity to sun

- Chlorpromazine collect in skin

- sunlight causes pigmentation changes – grayish-purple (look bruised)

- in eye, brown cornea and pigmented lens (possibly permanent impairment)

Agranulocytosis – 1.6% (with clozapine)

- reduced white blood cell count
- lowered resistance to infection
- can be fatal
- So weekly blood count is needed

# Neurological Side Effects of antipsychotics

REACTION	FEATURES	TIME OF MAXIMAL RISK	PROPOSED MECHANISM	TREATMENT
Acute dystonia	Spasm of muscles of <b>tongue, face, neck</b> , back; may mimic seizures; <i>not</i> hysteria	1 to 5 days	Unknown	Diphenhydramine, promethazine
Akathisia	<b>Motor restlessness</b> ; <i>not</i> anxiety or "agitation"	5 to 60 days	Unknown	Dec./change drug: antiparkinsonian agents, benzodiazepines or propranolol
Parkinsonism	<b>Bradykinesia, rigidity, tremor</b> , mask facies, shuffling gait	5 to 30 days	Antagonism of dopamine	Antiparkinsonian agents helpful- trihexyphenidyl, procyclidine, benztropines

REACTION	FEATURES	TIME OF MAXIMAL RISK	PROPOSED MECHANISM	TREATMENT
Neuroleptic malignant syndrome	Catatonia, stupor, fever, unstable BP, myoglobinemia; can be fatal	Weeks; can persist for days after stopping neuroleptic	Antagonism of dopamine	Stop neuroleptic immediately: dantrolene or bromocriptine may help: (cen. anticholinergic) not effective
Perioral tremor ("rabbit syndrome")	Perioral tremor (late variant of parkinsonism)	After months or years of treatment	Unknown	Antiparkinsonian agents often help
Tardive dyskinesia	Oral-facial dyskinesia; widespread choreoathetosis or dystonia	After months or years of treatment (worse on withdrawal)	Excess function of dopamine	Stop neuroleptics then Diazepam, Change to clozapine/olanzapine, (cen. anticholinergic) are even C/I

# Limitations Of Conventional Antipsychotics

- Approximately **one-third** of patients with schizophrenia **fail to respond**
- **Limited efficacy against**
  - Negative symptoms
  - Affective symptoms
  - Cognitive deficits
- High proportion of patients **relapse**
- **Side effects** and compliance issues

# Atypical antipsychotics

Clozapine

Olanzapine

Quetiapine

Risperidone

Iloperidone

Paliperidone

Ziprasidone

Lurasidone

Aripiprazole

Asenapine

Sertindole

Zotepine

# Clozapine

Selectively blocks dopamine D4 receptors, avoiding nigrostriatal pathway

- $\alpha$ -blockade
- $H_1$  -blockade
- **5-HT<sub>2</sub>** –blockade in cortex (which then acts to modulate some dopamine activity)
- Among **non-responders** to first generation meds or those who cannot tolerate side effects, about 30% **do respond to Clozapine**



# Clozapine

- Extrapiramidal side effects are minimal
- May help treat tardive dyskinesia
- **S/E- weight gain, hyperlipidemia, new onset DM, orthostatic hypotension effects, sedation**
- Increased risk for **seizures** (2-3%)
- **Agranulocytosis in 1%**

# Risperidone

- Blocks selective D2, norepinephrine, and 5-HT2
- Effective for positive and negative symptoms
- Fewer side effects than Clozapine
- Extrapyramidal side effects low
- No agranulocytosis risks
- Increased risk of stroke in elderly
- Sedation, weight gain, rapid heart beat, orthostatic hypotension, and elevated prolactin
- May cause anxiety/agitation (possible OCD)

# Olanzapine

- Improved negative symptom reduction
- Argued to be better than risperidone in extrapyramidal issues
- Does not cause prolactin elevation
- reduced agranulocytosis risks
- **Weight gain, hyperlipidemia, new onset DM**
- **Metformin** may be added to control these side effects

# Sertindole

- Concern about sudden cardiac death or episodes due to **cardiac arrhythmia** led to its **voluntary removal in 1998**
- Improved negative symptom reduction
- Low risk for extrapyramidal side effects – major advantage
- No sedation and very mild prolactin elevation– major advantages
- Shares orthostatic hypotension, tachycardia, and weight gain
- Common **side effects** are **rhinitis** and **reduced ejaculatory volume**

## Quetiapine

- No increased risks for extrapyramidal symptoms
- **sedation (sleepiness)**, **cataract**, orthostatic hypotension, weight gain
- Anticholinergic side effects (like older and Clozapine) – dry mouth, constipation
- Does not elevate prolactin

## Ziprasidone

- **No weight gain**
- May induce **cardiac arrhythmias**
- Also has **anxiolytic and antidepressant activity**

# Antipsychotics available as depot I.M.

- Aripiprazole lauroxil (every four to six weeks )
- Haloperidol
- Fluphenazine
- Risperidone
- Paliperidone

# Non- psychiatric Indications

- As **Antiemetics**
  - chlorpromazine, prochlorperazine, haloperidol**
- **Anaesthesia**
  - droperidol (with fentanyl)**
- **Intractable Hiccups**
  - chlorpromazine**
  - haloperidol**

# Points to remember

- Positive Symptoms( $\uparrow\uparrow$ DA)
- Negative Symptoms( $\downarrow\downarrow$ NMDA)
- Dopamine, Serotonin and Glutamate hypothesis of schizophrenia
- Neurological ADRs- Acute dystonia, Akathisia, Parkinsonism, Neuroleptic malignant syndrome, Perioral tremor, Tardive dyskinesia
- Non- psychiatric Indications- Antiemetics, Anaesthesia, Intractable Hiccups



# Bibliography

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Thank you