Neuroleptic (antipsychotic) drugs

Psychosis

Psychosis (from the Greek, *psyche*; mind/soul and *–osis*; abnormal condition or derangement) refer to an abnormal condition of the mind.

A syndrome of chronic disordered thinking and disturbed behavior.

The most severe psychiatric disorders; seriously inability to think, symptoms of false beliefs(delusions), abnormal sensation (hallucination), representative syndromes in this category include schizophrenia brief psychosis and delusion disorders.

Schizophrenia

Schizophrenia is a chronic mental disorder involving a breakdown in the relation between thought, emotion and behaviour leading to faulty perception, inappropriate actions and feelings withdrawal from reality and personal relationships in to fantasy and delusion, and sense of mental fragmentation.

Its one of the most important forms of psychiatric illness occurs with regular frequency nearly everywhere in the world in 1% of population because it affects young people (mostly around 16-25 years) is often chronic and is usually highly disabling. There is strong hereditary factor in its etiology and evidence suggestive of a fundamental biological disorder. Continuous signs of the disturbance for at least 6 months.

Clinical features of the disease are as follows:

- ❖ *Positive symptoms*:
  - Delusions.
  - Hallucinations.

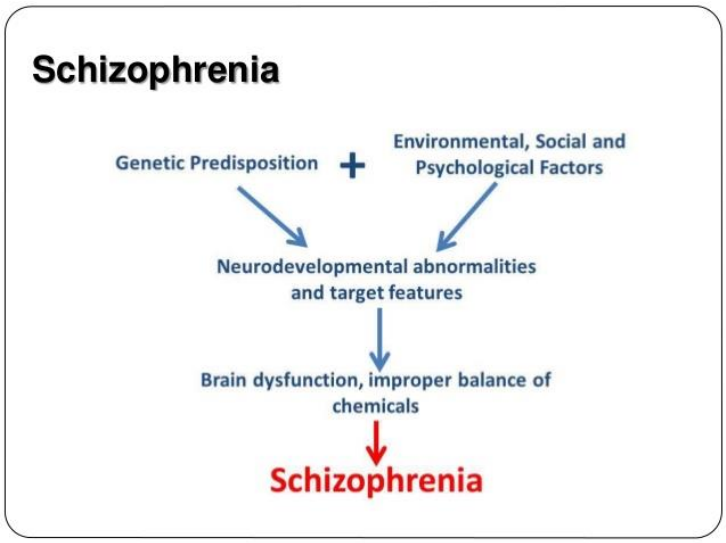
- Thought disorder (comprising wild trains of thought, delusions of grandeur, garbled sentences and irrational conclusions).
- Abnormal, disorganised behaviour (such as stereotyped movements, disorientation and occasionally aggressive behaviours).
- Catatonia (can be apparent as immobility or purposeless motor activity).

❖ *Negative symptoms:*

- Withdrawal from social contracts.
- Flattening of emotional response.
- Reluctance to perform everyday tasks.

❖ *Cognition:*

Deficits in cognitive function (e.g. attention, memory).



Neurochemical basis of Schizophrenia

➢ Dopamine:

Schizophrenia results from excess activity of dopamine neurotransmission in mesolimbic and mesocortical pathway. Amphetamine release dopamine in the brain and can produce in humans a behavioural syndrome reminiscent of an acute schizophrenic episode. Also, hallucination are a side effect of levodopa and dopamine agonists used for Parkinson's disease. Potent D2-receptor agonist such as bromocriptine produce similar effects in animals, these drugs like amphetamine, exacerbate the sympoms of schizophrenic patients.

➢ Glutamate:

NMDA receptor antagonists such as Phencyclidine, ketamine and dizocipline can produce positive, negative and cognitive deficit symptoms- in contrast to amphetamine which produce only positive symptoms. It has been therefore been postulated that schizophrenia may result from disruption of glutamatergic neurotransmission, evident as a reduction in the function of NMDA receptors, NMDA receptor hypofunction in the cortex may affect GBAergic interneurons and alter cortical processing, giving rise to cognitive impairment.

Antipsychotic

Antipsychotic also called neuroleptics or major tranquilizers) are used primarily to treat Schizophrenia, but they are also effective in other psychotic state including manic states with psychotic symptoms such as grandiosity, paranoia, and hallucination, delusion.

Classification of antipsychotic drugs

- First-genertion antipsychotic (low potency)

Chlorpromazine
Thioridazine

- First-generation antipsychotic (high potency)

Fluphenazine. Pimozide.
Haloperidol. Prochlorperazine.
Loxapine. Thiothixene.
Perphenazine. Trifluperazine.

- Second-generation antipsychotic

Aripiprazole Iloperidone Paliperidone
Asenapine Lurasidone Quetiapine
Clozapine Olanzapine Risperidone
Ziprasidone

First-generation antipsychotics:

Also called conventional, typical or traditional antipsychotics are competitive inhibitors at a variety of receptor but their antipsychotic effects reflect competitive blocking of D2 receptors. First-generation antipsychotics are more likely associated with movement disorders known as EPS, particularly drugs that bind tightly to dopaminergic neuroreceptors such as haloperidol.

Second- generation antipsychotic drugs:

Are also called atypical antipsychotics have a lower incidence of EPS than the 1st generation agents but are associated with a higher risk of metabolic side effects such as diabetes, hypercholesterolemia, and weight gain .The second generation drugs appear to owe their unique activity to blockade of both serotonin and dopamine and other receptors.

First choice agents for Schizophrenia used second generation of antipsychotic drugs (e.g Clozapine, Olanzapine, Risperidone, Quetiapine, Ziprasidone, aripiprazole) may have superior efficacy for negative symptoms and coginition.

Second generation of antipsychotic drugs cause few or no acutely occurring extrapyramidal side effects minimal or no propensity of Tardative Dyskinesia (TD) and less effect on serum Prolactine than the typical of antipsychotics.

Clozapine can produce bone marrow suppression, seizure and CV side effects such as orthostasis.

4 weeks at therapeutic doses than an alternative antipsychotic should be considered

Pharmacological Properties:

- Dopamine properties:

There are five subtypes of dopamine receptors in CNS; D1, D2, D3, D4, D5.

Antipsychotics produce catalepsy (reduce motor activity) by blockade of Dopamine receptors in basal ganglia.

Antipsychotics reverse hyperkinetics behaviors (increase locomotion and stereotyped behaviors) by blockade dopamine receptors in limbic areas.

Antipsychotics prevent the dopamine inhibition of prolactine release from pituitary by blockade of dopamine receptors in pituitary (Hyperprolactinemia).

All 1st generation and most of 2nd generation antipsychotic drugs block D2 dopamine receptors in the brain and the periphery.

- 5-Hydroxytyramine Receptors:

Drugs with 5-HT2A antagonism properties (e.g. Olanzapine and Risperidone) enhance dopamine release in the striatum by reducing the inhibitory effect of 5-HT. This will reduce EPS.

Clozapine has high affinity for D1, D4, 5-HT2, Muscarinic and α-adrenergic receptors, but also week dopamine D2 receptor antagonist.

Aripiprazole is a partial agonist at D2 and 5-HT1A receptors, as well as an antagonist of 5-HT2A receptors.

Quetiapine blocks D2 receptors more potently than 5-HT 2A receptors.

- Muscarinic Receptors:

Some 2nd generation drugs posses muscarinic antagonism properties (e.g. Olanzapine).It is suggested that there is normally balance between D2 receptors activation and muscarinic receptors activation.

Therapeutic Uses

1.Treatment of Schizophrenia: 1st generation antipsychotics are most effective in treating positive symptoms of schizophrenia. The a typical antipsychotics with 5-HT2A receptor-blocking activity may be effective especially in treating negative symptoms of schizophrenia.

2.Prevention of Nausea and Vomiting: Most commonly prochlorperazine are useful in treatment of drug induce nausea.

Most of antipsychotic drugs have antiemetic effects (with exception of Aripiprazole) that are mediated by D2 receptors of the chemotherapy trigger zone of the medulla.

3. Anticholinergic effects: Some of the antipsychotics, particularly thioridazine, chlorpromazine, clozapine and olanzapine produce anticholinergic effects. These effects include blurred vision, dry mouth (the exception is clozapine which increase salivation), confusion, constipation and urinary retention.

Pharmacokinetics:

Antipsychotic highly lipophilic and highly bound to plasma protein (92-98%) and largely metabolize by cytochrome P450 pathways.The plasma half-life of most antipsychotic drugs is 15-30 h, clearance depending entirely on hepatic transformation by a combination of oxidative and conjugative reactions.

Resperidone and its active metabolite are metabolized by CYP2D6.

After dosage stabilization, most antipsychotic(except quetiapine and ziprasidone) can be dosed once daily.

Unwanted effects

- Extrapyramidal effects:

Antipsychotic drugs produce two main kinds of motor disturbance in humans; *Acute dystonias and Tardative dyskinesias,* Collectively termed extrapyramidal side effects.

- *Acute dystonias* : are involuntary movements (restlessness, muscle spasm, protruding tongue, fixed upward gaze, neck muscle spasm), often accompanied by symptoms of Parkinson's disease.
- *Tardative dyskinesia:* involuntary movements, often of the face and tongue, but also trunk and limbs, which can severely disabling.

Long-term study of Olanzapine, risperidone, quetiapine and ziprasidone concluded that they too can induce EPS. Even aripiprazole which is D2 partial agonist, has been reported to produce this unwanted effect.

- Endocrine effects:

Dopamine that act physiologically via D2 receptors to inhibit prolactin secretion. Blocking D2 receptors by antipsychotic drugs can therefore increase plasma prolactin concentration resulting in breast swelling, pain and lactation which can occur in men as well as in women.

- Because of its D2 receptor partial agonist action aripiprazole unlike other antipsychotic drugs reduce prolactin secretion. Other less pronounced endocrine changes including decrease of GH secretion.

- Other unwanted effects:

- Antihistamine (H1) activity is a property of chlorpromazine and contributes to their sedative and antiemetic properties.
- Block of muscarinic receptors produce a variety of peripheral effects, including blurred vision and increase IOP, dry mouth and

eyes, constipation and urinary retention, also be beneficial in relation to EPS.

Blocking α-adrenoreceptors causes *Orthostatic hypotension.*

Weight gain is a common and troublesome side effect. Increase risk of diabetes and CVD occur with 2nd generation antipsychotic drugs. These effects are related to their antagonistic actions at H1, 5-HT and muscarinic receptors.

Antipsychotic drugs can prolong QT interval in the heart giving rise to arrhythmia and risk of sudden death. Various idiosyncratic and hypersensitivity reactions can occur, the most important being the following:

**Jaundice* occur with chlorpromazine. The juandice is usually mild associated with elevated Serum alkaline phosphatase.

**Leukopenia and agranulocytosis:* are rare but potentially fatal and occur in 1st few weeks of treatment. Much higher (1-2%) with clozapine requires regular monitoring of blood cell counts.

* *Urticarial skin reactions* are common but usually mild.

* *Antipsychotic malignant syndrome* is a rare but serious complication similar to malignant hyperthermia. Muscle rigidity is accompanied by a rapid rise in body temperature and mental confusion.

Drug	Notes
(First generation)	
Chlorpromazine	Moderate to high potential for EPS and wight gain, orthostasis, sedation, antimuscarinic.
Fluphenazine	Oral formulation has a high potential for EPS;Low to moderate potential for muscarinic effects: Low potential for weight gain, sedation and orthostasis. Long acting injectable formulation administer every 2-3 weeks.
Haloperidol	High potential for EPS; Low potential for orthostsis or antimuscarinic side effects; low potentail for weight gain or sedation. Long acting injectable formulation administer every 1 month
(Second generation)	
Aripiprazole	Low potential for EPS, weight gain, sedation and antimuscarinic effects. Used for treatment bipolar disorder, autistic in children and adjunctive treatment for major depression.
Asenapine (available as sublingual)	Low potential for EPS and wight gain. Low to moderate potential for sedation and orthostasis. Used for bipolar disorder
Clozapine	Very low potential for EPS, high potential for weight gain, sialorrhea, orthostasis,sedation and antimuscarinic effects.

	Risk for seizure, myocarditis, granulocytosis.
Olanzapine	Low potential for EPS,orthostasis. Moderate to high potential for weight gain and sedation. Approved for treatment for bipolar disorder. Long acting injectable administered every 2-4 weeks.
Quetiapine	Low potential for EPS, Moderate potential for weight gain and orthostasis, moderate to high potential for sedation. Approved for treatment for bipolar disorder and adjunctive treatment for major depression.
Reseridone	Low to moderate potential for EPS, Weight gain, orthostasis, sedation. Approved for treatment for bipolar disorder, also approved for autistic disorder. Long acting injectable administered every 2 weeks.
Ziprasidone	Low potential for EPS minimal weight gain. CI: history with cardiac arrythmias. Used for treatment of bipolar depression