SCHIZOPHRENIA

Definition:-

It is a heterogenous syndrome of disorganized and bizare thoughts, delusions, hallucinations, inappropriate affect & impaired psychosocial functioning.

It is most complex and challenging of psychiatric disorders.

It is a debilitating and emotionally devasting illness with long-term impact on patient's lives.

Etiology - Multifactors

1) During Pregnancy and Birth :-

a) Utero disturbance
   i.e during 2nd trimester of pregnancy
   - due to abnormal neuronal migration
   - Abnormalities in cell shape, position, symmetry connectivity
   ↓
   Causes "schizophrenic lesions"
   - If upper respiratory tract infections it leads to higher risk of schizophrenia

b) Maternal stress –

[May be due to external & internal noxious events i.e Malnutrition infection]

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glucocorticoids circulate in utero

↓

Risk factor for getting schizophrenia.

c) Low birth weight [i.e < 2.5 kg]

2.) Brain anatomy :-

- Decreased cortical thickness
- Decreased ventricular size (lateral + third)
- Morphologic abnormalities involving in the temporal, frontal, parietal lobes and subcortical structures
- Decreased neuronal volume & density
- Decreased synaptic connections → Decreased in Synaptophysin.
- Alterations in either cerebral perfusion (or) glucose metabolism in frontal, temporal and basal ganglia.
- Mostly affected areas - prefrontal & temporal lobes (-ve symptoms) (+ve symptoms)

3) Genetics :-

- If both the parents have schizophrenia then 40% chances of producing in offsprings.

Clinical features

2 types - Type-1 (Positive features)
Type-2 (Negative features)

Type-1 (Positive features):-

1.) Cognitive - Distorted or irrational reasoning reducing insight
Inattention, poor memory
poor problem solving and abstract thinking

2.) Belief - Delusions
Delusional perception
Derealisation
Depersonilization

3) Perception - Hallucinations
- usually auditory
- also visual
⊥ less common - tactile
gustatory
olfactory

4.) Mood - Inappropriate emotional responses

5.) Behaviour - Bizarre, irrational
occasionally aggressive
rarely violent

Type - 2 (Negative features)

1) Mood - Blunting (flattening) of affect

2) Behaviour - withdrawn, antisocial, apathetic, poor-self-care, poverty of speech (poor) anhedonia, avolition. anhedonic

Pathophysiology

This can be clearly explained by the dopaminergic pathways.

4 pathways

1. Mesolimbic pathways
2. Mesocortical pathways
3. Nigrostriatal pathways
4. Tuberoinfendilubar pathways

} normal in schizophrenic patient

Mesolimbic pathways:-

Dopamine originates in the ventral segmented area and innervates several structures of the limbic system including nucleus accumbens

This pathway is important for memory and for motivating behaviours

Mesocortical dopamine pathway:-

Dopamine also originates in ventral tegmentum area but projects to the frontal cortex and surrounding structures.

Evidences indicates that a malfunction in this pathway might be the cause of some of the symptoms of schizophrenia such as hallucination and disordered thinking

Ventral tegmental area to the prefrontal cortex are involved in the negative & cognitive symptoms.

Nigrostriatal pathway:-

It starts from substantia nigra to the striatum which is involved in motor control.

Degeneration of neurons in this pathway is associated with the trembling and muscular rigidity symptoms of parkinsonism.

This pathway is normal in schizophrenia.

Tuberoinfundibular pathway:-

This pathway connects hypothalamus to pituitary gland, where it influences the secretion of hormones such as prolactin

In untreated schizophrenia this is normal.

The +ve symptoms are possibly more closely associated with DA receptor hyperactivity in the mesocaudate

The -ve symptoms & cognitive symptoms are closely related to DA receptor hypofunction in prefrontal cortex.

NMDA receptor hypothesis of schizophrenia

A major hypothesis of schizophrenia proposes that numerous genetic risk factors converge on the NMDA receptor for the neurotransmitter glutamate

Theoretically

Abnormalities in glutamate neurotransmission

↓

hypofunction of NMDA receptors

↓

Abnormal DA activity associated w schizophrenia symptoms.

- This pathway projects from cortical putamen neuron to dopamine neurons in the ventral tegmented area.

- This pathway, descending glutamate pathway act as a break on the mesolimbic dopaminergic pathway.

– It results in tonic inhibition of DA release from mesolimbic pathway

Descending cortico-brainstem glutamate neuron

hypoactive of NMDA receptors in VTA

↓

act on Mesolimbic pathway

↓

Causes hyperactive and +ve symptoms of psychosis

accelerates to Mesocortical DA neurons

↓

has NMDA receptors hypoactivity

↓

lose excitatory drive and become hypoactive (cognitive & -ve symptoms

Pathways for the development of Schizophrenia

Genetic predisposition → Neurodevelopmental abnormalities → Neurocognitive impairment → Frank Psychos

Neurocognitive impairment: Social anxiety, Isolation, odd ideas

obstetric complications & other early insults affecting CNS → Neurodevelopmental abnormalities

Abuse of dopaminergic drugs; social stress/Isolation → Frank Psychos

Schizophrenia pharmacotherapy algorithm

Stage 1A

First-break schizophrenia

Any Antipsychotic monotherapy except clozapine

Stage 1B

previously treated with an antipsychotic drug for schizophrenia & treatment is being restarted

Any Antipsychotic drug except clozapine & an antipsychotic that previously produced poor efficacy (or) intolerance shouldn't be used.

→ **Stage-2** ←

Inadequate clinical response with antipsychotic used in stage 1A or 1B

An Antipsychotic monotherapy except clozapine not used in stage 1A & 1B. Clozapine may be considered in suicidal patient.

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Stage-3

Patient has had inadequate clinical response with two appropriate antipsychotic trials clozapine monotherapy is recommended.

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Stage - 4

No adequate treatment response τ clozapine.

Alternative antipsychotic monotherapies may be as good as antipsychotic combination.

NOTE:- Use a longacting injectable antipsychotic at either stage 3 or 4 for poor patient adherence.

Treatment

Goals

1. Minimize symptoms of schizophrenia
2. Improve quality of life and social/occupational functioning
3. prevent relapse and hospitalization
4. minimize ADR of medications
5. Prevent suicide attempts or self harm.

Pharmacological management:-

1) Antipsychotic drugs

2) Non - Antipsychotic drugs

Antipsychotic drugs

Two generations — 1. First generation (or) Typical
2. second generation (or) Atypical

Atypical antipsychotic drugs are more preffered than typical antipsychotic drugs as it is owing to less risk of Extra pyramidal symptoms.

I. Typical Antipsychotic drugs:-

- Also called as Conventional antipsychotic (or) dopamine receptor antagonist.
- These agents block central dopamine receptors particularly D_2 receptors
- These agencies classified based on their relative ability to block dopamine (D_2) receptor like-

a) high potency — Haloperidol, Fluphenazine, Thiothixene

b) Mild potency — Trifluoperazine, Perphenazine, Loxapine, Molindone

c) Low potency :- Chlorpromazine
Thioridazine.

Drug Name	Initial dose mg/day	Maintainence dose mg/day	ROA	$t_{1/2}$	t_{max}	B.A
1. Haloperidol	2-5 mg	2-20	PO	12-30 hrs	24 hrs	40-70%
2. Haloperidol decanoate	50 mg/ml once Monthly	Use tp 25% at 2nd and 3rd Month	I.M	21 days		
3. Loxapine	20 mg	50-150 mg	P.O			
4. Fluphenazine	5 mg	5-20 mg	P.O	14-24 hrs		20-50%
5. Fluphenazine decanoate	12.5 mg/ml per week. for 4-6 weeks (acute ill) 25 mg/ml per week for more ill pt	~~25~~	I.M	14.2 ± 2.2 days		
6. Chlorprama-zine	50-150 mg	300-1000 mg	P.O	8-35 hrs		10-30%
	25-50 mg single dose		I.M			

II. Atypical Antipsychotic drugs

- Also called as serrotonin dopamine antagonists (D_2) (or) second generation antipsychotics
- Also blocks 5-HT2A receptors
- Blocks D_2 lesser than the 5-HT2A

Ex:- Clozapine
Risperidone
olanzapine
Quetiepine

Drug name	Initial dose (mg/day	Maintainence dose (mg/day	ROA	$t_{1/2}$	tmax	B.A
1) Risperidone	1-2 mg	2-8 mg	P.O	3-24 hrs.		68%.
2) Risperidal Consta	25 mg every 2 weeks	along T ord Medication for 3 weeks (max → 50 mg/day dose	I.M	3-6 days		
3) Olanzapine	5-10 mg	10-20 mg	P.O	20-70 hrs.		80%.
4) Olanzapine	2.5-10 mg per day		I.M			
5) Quetiepine	50 mg/day	300-800 mg/day	P.O	6.88 hrs		9±4%.

Drug name	Initial dose (mg/day)	maintainence dose (mg/day)	ROA	$t_{1/2}$	t_{max}	B.A.
6) Paliperidone (ER)	3-6	3-12	P.O	23 hrs		28%
7) paliperidone palmitate	234 mg day 1	156 mg a week later ↓ 117 mg/0.75ml Monthly	I.M	25-49 days		
8) Clozapine	25 mg	12.5 - 800 mg/day	P.O	11-105 hrs		12-81%

Clozapine test dose :-

12.5 mg given at bed time, if it doesn't produce hypotension

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then 25 mg at bed time recommended initial dose of 3days

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increased in 25-50mg/day increments every 3days untill 300 mg/day is reached

Note:- Monitor clozapine serum conentration - not exceed 600mg/day.

Non-Antipsychotic Agents:-

1) Benzodiazepines:-

→ Lorazepam - 2mg po/IM/IV

Max dose → 1-3 mg/day

$t_{1/2}$ → 12-15 hrs

Tmax → 60-90 mins

- reduce the agitation behaviour
- In combination ~ Haloperidol for rapid control of agitation & psychosis

2) Lithium:-

- Monotherapy (or) adjunctive with antipsychotic drugs.
- dose of lithium should be sufficient to obtain a blood level in the range of 0.8 to 1.2 mEq/L

3) Anticonvulsants:-

Carbamazepine

Valproate.

4) Propranolol:-

Combination ~ antipsychotic drugs

Starting up → 40-80mg BD

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increased everyday untill intolerable ADR occurs.

usually — 240mg/day for 2 months

Adverse effects

1) Endocrine system :-

1) Hyperprolactinemia — leads to gynecomastia, galactorrhea
Menstrual irregularities, ↓sed libido
Sexual dysfunction
weight gain
Type-2 DM

2) CVS : -

- orthostatic hypotension
- ECG changes
- elevation in serum TG and cholestrol

3) ANS: -

dry mouth, constipation, blurred vision,
urinary retention, impaired memory

4) Extrapyramidal symptoms :-

a) Dystonia (abnormal tonicity)
b) Akathisia
c) Pseudoparkinsonism
d) Tardive dyskinesia

5) sedation and cognition

6) Seizures

7) Neuroleptic malignent syndrome

8) Hematologic system — leucopenia
agranulocytosis

9) Hepatic system :-

Cholestatic hepatocanalicular jaundice

10) Genitourinary system:-

- Sexual dysfunction
- Urinary retention

11) Dermatological system :-

allergic reactions are rare.

12) Miscellaneous side effects :-

diarrhoea and drooling.

Non-pharmacologic therapy

Psychosocial rehabilitation programs include

- Case management
- psychoeducation
- Targeted cognitive therapy
- Basic living skills
- Social skills training
- Basic education
- work programmes
- Housing and financial support