Schizophrenia

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Schizophrenia

- It is not a single disease but a group of disorders with heterogeneous etiologies.
- Found in all societies and countries with equal prevalence & incidence worldwide.
- A life prevalence of 0.6 – 1.9 %
- Annual incidence of 0.5 – 5.0 per 10,000
- Peak age of onset are 10-25 years for ♂ & 25-35 years for ♀
Etiology

Exact etiology is unknown.

1- Stress-Diathesis Model:

- Integrates biological, psychosocial and environmental factors in the etiology of schizophrenia.
- Symptoms of schizophrenia develop when a person has a specific vulnerability that is acted on by a stressful influence.
2- Neurobiology

* Certain areas of the brain are involved in the pathophysiology of schizophrenia: the limbic system, the frontal cortex, cerebellum, and the basal ganglia.

a- Dopamine Hypothesis;
  Too much dopaminergic activity (whether it is ↑ release of dopamine, ↑ dopamine receptors, hypersensitivity of dopamine receptors to dopamine, or combinations is not known).

b- Other Neurotransmitters;
  Serotonin, Norepinephrine, GABA, Glutamate & Neuropeptides
SOME SCIENTISTS have proposed that too much dopamine leads to symptoms emanating from the basal ganglia and that too little dopamine leads to symptoms associated with the frontal cortex. Insufficient glutamate signaling could produce those same symptoms, however.

IN THE FRONTAL CORTEX, where dopamine promotes cell firing (by acting on D1 receptors), glutamate’s stimulatory signals amplify those of dopamine; hence, a shortage of glutamate would decrease neural activity, just as if too little dopamine were present.

IN THE BASAL GANGLIA, where dopamine normally inhibits cell firing (by acting on D2 receptors on nerve cells), glutamate’s stimulatory signals oppose those of dopamine; hence, a shortage of glutamate would increase inhibition, just as if too much dopamine were present.

IN THE REST OF THE CORTEX, glutamate is prevalent, but dopamine is largely absent.

ALFRED T. KAMAjian
c- Neuropathology;

Neuropathological and neurochemical abnormalities have been reported in the brain particularly in the limbic system, basal ganglia and cerebellum. Either in structures or connections.
THE BRAIN IN SCHIZOPHRENIA

MANY BRAIN REGIONS and systems operate abnormally in schizophrenia, including those highlighted below. Imbalances in the neurotransmitter dopamine were once thought to be the prime cause of schizophrenia. But new findings suggest that impoverished signaling by the more pervasive neurotransmitter glutamate—or, more specifically, by one of glutamate’s key targets on neurons [the NMDA receptor]—better explains the wide range of symptoms in this disorder.

**BASEAL GANGLIA**
Involved in movement and emotions and in integrating sensory information. Abnormal functioning in schizophrenia is thought to contribute to paranoia and hallucinations. (Excessive blockade of dopamine receptors in the basal ganglia by traditional antipsychotic medicines leads to motor side effects.)

**AUDITORY SYSTEM**
Enables humans to hear and understand speech. In schizophrenia, overactivity of the speech area [called Wernicke’s area] can create auditory hallucinations—the illusion that internally generated thoughts are real voices coming from the outside.

**FRONTAL LOBE**
Critical to problem solving, insight and other high-level reasoning. Perturbations in schizophrenia lead to difficulty in planning actions and organizing thoughts.

**OCCIPITAL LOBE**
Processes information about the visual world. People with schizophrenia rarely have full-blown visual hallucinations, but disturbances in this area contribute to such difficulties as interpreting complex images, recognizing motion, and reading emotions on others’ faces.

**HIPPOCAMPUS**
Mediates learning and memory formation, intertwined functions that are impaired in schizophrenia.

**LIMBIC SYSTEM**
Involved in emotion. Disturbances are thought to contribute to the agitation frequently seen in schizophrenia.

ALFRED T. KAMAJIAN
Early and Late Gray Matter Deficits in Schizophrenia

Earliest Deficit

5 Years Later (Same Subjects)

STG  DLPFC

Average Deficit
0%
-5%
-10%
-15%
-20%

Thompson et al., 2001
d- Psychoneuroimmunology;
↓ T-cell interleukin-2 & lymphocytes, abnormal cellular and humoral reactivity to neurons and presence of antibrain antibodies.
These changes are due to neurotoxic virus ? or endogenous autoimmune disorder ?

e- Psychoneuroendocrinology;
Abnormal dexamethasone-suppression test
↓ LH/FSH
A blunted release of prolactin and growth hormone on stimulation.
3- Genetic Factors

- A wide range of genetic studies strongly suggest a genetic component to the inheritance of schizophrenia that outweights the environmental influence.
- These include: family studies, twin studies and chromosomal studies.
Rates of Schizophrenia Among Relatives of Schizophrenic Patients*

- Parents
- Children
- Children - both parents schizophrenic
- Brothers and sisters
- Brothers and sisters - neither parent schizophrenic
- Brothers and sisters - one parent schizophrenic
- Fraternal twins of opposite sex
- Fraternal twins of same sex
- Identical twins
- Uncles and aunts
- Nephews and nieces
- Grandchildren
- Half brothers/sisters
- First cousins
- General population

* Based on Slater and Cowie (1971), with the exception of twin data from Shields and Slater (1975). Adapted, with permission, from Tsuang and Vandermey (1980).
Schizophrenia is mostly caused by various possible combinations of many different genes (which are involved in neurodevelopment, neuronal connectivity and synaptogenesis) plus stressors from the environment conspiring to cause abnormal neurodevelopment. There is also abnormal neurotransmission at glutamate synapses, possibly involving hypofunctional NMDA receptors.

**Table.**

**Susceptibility Genes for Schizophrenia**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysbindin</td>
<td>Erb-B4</td>
</tr>
<tr>
<td>Neuregulin</td>
<td>FEZ1</td>
</tr>
<tr>
<td>DISC-1</td>
<td>MUTED</td>
</tr>
<tr>
<td>DAOA</td>
<td>MRDS1</td>
</tr>
<tr>
<td>DAA0</td>
<td>BDNF</td>
</tr>
<tr>
<td>RGS4</td>
<td>Nur77</td>
</tr>
<tr>
<td>COMT</td>
<td>MA0-A</td>
</tr>
<tr>
<td>CHRNA7</td>
<td>Spinophylin</td>
</tr>
<tr>
<td>GAD1</td>
<td>Calcyon</td>
</tr>
<tr>
<td>GRM3</td>
<td>Tyrosine hydroxylase</td>
</tr>
<tr>
<td>PPP3CC</td>
<td>Dopamine$_2$ receptor</td>
</tr>
<tr>
<td>PRODH2</td>
<td>Dopamine$_3$ receptor</td>
</tr>
<tr>
<td>AKT1</td>
<td></td>
</tr>
</tbody>
</table>

DISC-1=disrupted in schizophrenia-1; DAOA=D-amino acid oxidase activator (G72/G30); DAA0=D-amino acid oxidase; RGS4=regulator of G-protein signalling 4; COMT=catechol O methyl transferase; CHRNA7=α-7 nictonic cholinergic receptor; GAD1=glutamic acid decarboxylase 1; GRM3=glutamate receptor, metabotropic 3; BDNF=brain derived neurotrophic factor; MAO-A=monoamine oxidase A.

4- Psychosocial Factors;

- In family dynamics studies, no well-controlled evidence indicates specific family pattern plays a causative role in the development of schizophrenia.

- High Expressed Emotion family: increase risk of relapse.
Weight of different RF: Family history comes first
Diagnosis

# DSM-IV-TR Diagnostic Criteria for Schizophrenia:
A- ≥ two characteristic symptoms
  1- Delusions
  2- Hallucinations
  3- Disorganized speech
  4- Disorganized behavior
  5- Negative symptoms
B- Social / Occupation dysfunction
C- Duration of at least 6 months
D- Schizoaffective & mood disorder exclusion
E- Substance / General medical condition exclusion
F- Relationship to pervasive developmental disorders
Subtypes of Schizophrenia

- Paranoid type
- Disorganized type
- Catatonic type
- Undifferentiated type
- Residual type
Clinical Features

- No clinical sign or symptom is pathognomonic for schizophrenia
- Patient's history & mental status examination are essential for diagnosis.
- Premorbid history includes schizoid or schizotypal personalities, few friends & exclusion of social activities.
- Prodromal features include obsessive compulsive behaviors
- Picture of schizophrenia includes positive and negative symptoms.
- Positive symptoms like: delusions & hallucinations.
- Negative symptoms like: affective flattening or blunting, poverty of speech, poor grooming, lack of motivation, and social withdrawal.
Cognitive deficits in schizophrenia

Multiple Mechanisms for Cognitive Dysfunction in Schizophrenia

- 5-HT
- Dopamine
- Abnormal Connectivity
- Acetylcholine
- Neurodegeneration

Cognitive Deficits Predict Functional Outcomes

- Learning and memory
- Executive function
- Attention

- School and occupational function
- Social function
- Activities of daily living

Green 1996; Velligan et al 1997
Mental status examination

- Appearance & behavior (variable presentations)
- Mood, feelings & affect (reduced emotional responsiveness, inappropriate emotion)
- Perceptual disturbances (hallucinations, illusions)
- Thought:  Thought content (delusions)
  Form of thought (looseness of association)
  Thought process (thought blocking, poverty of thought content, poor abstraction, perseveration)
- Impulsiveness, violence, suicide & homicide
- Cognitive functioning
- Poor insight and judgment
Course

- Acute exacerbation with increased residual impairment
- Full recovery: very rare
- Longitudinal course: downhill
## Prognosis

<table>
<thead>
<tr>
<th>Good P.F</th>
<th>Poor P.F</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Late age of onset</td>
<td>1. Young age of onset</td>
</tr>
<tr>
<td>2. Acute onset</td>
<td>2. Insidious onset</td>
</tr>
<tr>
<td>3. Obvious precipitating factors</td>
<td>3. Lack of P.F.</td>
</tr>
<tr>
<td>4. Presence of mood component</td>
<td>4. Multiple relapses</td>
</tr>
<tr>
<td>5. Good response to Tx</td>
<td>5. Low IQ</td>
</tr>
<tr>
<td>6. Good supportive system</td>
<td>6. Poor premorbid personality</td>
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<td></td>
<td>7. Negative symptom</td>
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<tr>
<td></td>
<td>8. Positive family history</td>
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## Differential Diagnosis

<table>
<thead>
<tr>
<th>Nonpsychiatric disorders:</th>
<th>Psychiatric disorders:</th>
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<tbody>
<tr>
<td>Substance-induced disorders</td>
<td>Schizophreniform disorder</td>
</tr>
<tr>
<td>Epilepsy (TLE)</td>
<td>Brief psychotic disorder</td>
</tr>
<tr>
<td>CNS diseases</td>
<td>Delusional disorder</td>
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<tr>
<td>Trauma</td>
<td>Affective disorders</td>
</tr>
<tr>
<td>Others</td>
<td>Schizoaffective disorder</td>
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<tr>
<td></td>
<td>Personality disorders (schizoid, schizotypal &amp; borderline personality)</td>
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<tr>
<td></td>
<td>Malingering &amp; Factitious disorders</td>
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</tbody>
</table>
Treatment

What are the indications for hospitalization?
Diagnostic purpose
Patient & other's safety
Initiating or stabilizing medications
Establishing an effective association between patient & community supportive systems
Biological therapies

- Antipsychotic medications are the mainstay of the treatment of schizophrenia.
- Generally, they are remarkably safe.
- Two major classes:
  - Dopamine receptor antagonists (haloperidol, chlorpromazine)
  - Serotonin-dopamine receptor antagonists (Risperidone, clozapine, olanzapine).
- Other drugs:
  - Anticonvulsants
  - Lithium
  - Benzodiazepines
- Depot forms of antipsychotics eg. Risperidone Consta is indicated for poorly compliant patients.
- Electroconvulsive therapy (ECT) for catatonic or poorly responding patients to medications
Pharmacological Treatment Algorithm
Adapted from the Maudsley prescribing Guidelines (Taylor et al, 2005)
## Common side effects of antipsychotic medication (Taylor et al, 2005)

<table>
<thead>
<tr>
<th>First generation antipsychotics</th>
<th>Second generation antipsychotics</th>
<th>Clozapine</th>
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<tbody>
<tr>
<td>Extrapyramidal effects</td>
<td>Olanzapine</td>
<td>Sedation</td>
</tr>
<tr>
<td>Dystonia</td>
<td>Weight gain</td>
<td></td>
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<tr>
<td>Pseudoparkinsonism</td>
<td>Sedation</td>
<td></td>
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<tr>
<td>Akathisia</td>
<td>Glucose intolerance and frank</td>
<td></td>
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<tr>
<td>Tardive dyskinesia</td>
<td>diabetes mellitus</td>
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<tr>
<td></td>
<td>Hypotension</td>
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<tr>
<td>Sedation</td>
<td>Risperidone</td>
<td>Hypersalivation</td>
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<tr>
<td>Hyperprolactinaemia</td>
<td>Hyperprolactinaemia</td>
<td>Constipation</td>
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<tr>
<td></td>
<td>Hypotension</td>
<td></td>
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<tr>
<td></td>
<td>EPS at higher doses</td>
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<tr>
<td></td>
<td>Sexual dysfunction</td>
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<tr>
<td>Reduced seizure threshold</td>
<td>Amisulpiride</td>
<td>Reduced seizure threshold</td>
</tr>
<tr>
<td>Postural hypotension</td>
<td>Hyperprolactinaemia</td>
<td>Hypo &amp; hypertension</td>
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<tr>
<td></td>
<td>Insomnia</td>
<td></td>
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<tr>
<td>Anticholinergic effects</td>
<td>Extrapyramidal effects</td>
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<tr>
<td>Blurred vision</td>
<td>Quetiapine</td>
<td>Tachycardia</td>
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<tr>
<td>Dry Mouth</td>
<td>Hypotension</td>
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<tr>
<td>Urinary Retention</td>
<td>Dyspepsia</td>
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<tr>
<td>Neureleptic malignant syndrome</td>
<td>Drowsiness</td>
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<tr>
<td>Weight gain</td>
<td></td>
<td></td>
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<tr>
<td>Sexual dysfunction</td>
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<tr>
<td>Cardio-toxicity</td>
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<tr>
<td>(including prolonged QTc)</td>
<td>Rare serious side effects</td>
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<tr>
<td></td>
<td>Neutropenia 3%</td>
<td></td>
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<tr>
<td></td>
<td>Agranulocytosis 0.8%</td>
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<tr>
<td></td>
<td>Thromboembolism</td>
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<tr>
<td></td>
<td>Cardiomyopathy</td>
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<tr>
<td></td>
<td>Myocarditis</td>
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<tr>
<td></td>
<td>Aspiration pneumonia</td>
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</tbody>
</table>


Psychosocial therapies

Social skills training
Family oriented therapies
Group therapy
Individual psychotherapy
Assertive community treatment
Vocational therapy
Thank you