The Current State of Schizophrenia

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Agenda

- History
- Etiology/Pathophysiology
- Signs and Symptoms
- Treatment
- Comorbidities

History

- 1887 – First identified as a mental illness by Dr. Emil Kraepelin: “Dementia Praecox”
- 1911 – Eugène Bleuler coined the term “Schizophrenia”
- 1952 – Dr. Henri Laborit, a French Surgeon, discovers chlorpromazine
- 1954 – FDA approves Chlorpromazine
- 1980s – Brain imaging techniques show structural and functional abnormalities in schizophrenia patients
- 1980s – Second Generation Antipsychotics first introduced with Clozapine

Source:

Etiology and Pathophysiology

- Dopamine Hypothesis
- Glutamate Hypothesis
- Inflammatory Hypothesis
- Environmental link
- Genetic Link

Dopamine Hypothesis

- Increased Dopamine in the mesolimbic pathway
  - Hypertimulation of D2 receptors
  - Positive Symptoms
- Decreased Dopamine in the mesocortical pathway
  - Hypostimulation of D1 receptors
  - Negative symptoms and Cognitive Impairment


Glutamate Hypothesis

- Stemmed from observations of Phencyclidine ("PCP")
- Glutamate regulates the mesocortical and mesolimbic dopamine pathways
- Glutamate reduction leads to dopamine hyperactivity in the mesolimbic pathway and hypoactivity in the mesocortical, nigrostriatal, and tuberoinfundibular pathways
- A 2009 study found a reduction in glutamate receptors in the dorsolateral prefrontal cortex in schizophrenic subjects

The Role of Genetics

- Strong genetic component supported by twin studies
- Polygenic
  - Genome-wide association studies: 108 gene loci implicated in schizophrenia
    - Many identified loci were associated with D2 receptors and glutamatergic neurotransmission and synaptic plasticity
    - Many loci had strong associations in tissues with immune function


Role of the Environment

- Prenatal Infection: A study found that maternal influenza during the first trimester results in a sevenfold increase in the risk of schizophrenia for the offspring
- Maternal Malnutrition
- Obstetric complications
- Urbanicity
- Geographic (Northern Hemisphere)
- Cannabis Exposure


Inflammatory Hypothesis

- Psychosis has been shown to cause neuro-inflammation
- Many studies have shown increased pro-inflammatory cytokines
- Several studies have found that adding an anti-inflammatory agent to an antipsychotic can improve therapeutic response, particularly during first episode psychosis

Signs and Symptoms

- Prodromal Period
- Positive and Negative Symptoms
- Cognitive Impairment

Prodromal Period

- 80% of schizophrenia patients initially experience changes in thought perception, thought process, and thought content
- Sub-delusional changes: i.e. becoming suspicious
- Difficulty following conversation, easy distractability, poor attention
- Avolition and anhedonia
- The largest decline in social and occupational function occurs during the prodromal period

Positive and Negative Clusters

<table>
<thead>
<tr>
<th>Positive Cluster</th>
<th>Negative Cluster</th>
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<tbody>
<tr>
<td>Hallucinations</td>
<td>Flat Affect</td>
</tr>
<tr>
<td>Delusions</td>
<td>Avolition</td>
</tr>
<tr>
<td>Disorganized thought and speech</td>
<td>Alogia</td>
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</tbody>
</table>
Hallucinations

- Auditory
- Visual
- Somatic
- Olfactory
- Gustatory

Delusions

- Persecutory
- Grandiose
- Somatic
- Erotomanic
- Thought Broadcasting

Disorganized

Thought Process and Speech

- Blocking
- Circumstantiality
- Tangentially
- Preservation
- Loosening of associations
- Ideas of Reference

- Clanging
- Neologisms
- Echolalia
- Flight of Ideas
- Derailment
Cognitive Deficits

- Poor Executive Functioning
- Trouble focusing and paying attention (sensory processing data)
- Deficits in working memory
- Slower Processing Speed


Treatment

- FGAs and SGAs
- First Episode Psychosis
- Maintenance Therapy
- Treatment Resistance/Treatment Failure
- Non-pharmacologic treatment

Treatment

First Generation Antipsychotics
- Chlorpromazine
- Haloperidol
- Fluphenazine
- Thioridazine

Second Generation Antipsychotics
- Aripiprazole
- Asenapine
- Clozapine
- Risperidone
- Lurasidone
- Brexpiprazole
- Olanzapine
- Paliperidone
- Quetiapine
- Ziprasidone
- Ziprasidone
First Episode Psychosis

- Odds of achieving remission decrease by 15% for each year psychosis goes untreated
- Second Generation Antipsychotics are recommended as first line treatment over First Generation Antipsychotics
- Dosages should be in the lower half of the treatment range and lower than dosages used in multi-episode schizophrenia
- Treatment guidelines and experts recommend 1-2 years of treat in FEP before discontinuation
- Studies are limited on the use of Long Acting Injectable Antipsychotics for FEP, but have shown improved symptom control, adherence to medication, reduced relapse rates and re-hospitalization, less reduction in white brain matter volume, and no difference in EPS or prolactin-associated side effects


Maintenance Therapy

- Second-generation antipsychotics are first line treatment
- Use the lowest dose that was effective at reducing positive symptoms in the acute phase of treatment
- Patients who experience continuous symptom relief should continue antipsychotic treatment in order to maintain symptom relief and reduce risk of relapse


Long Acting Injectables

- Haloperidol
- Fluphenazine
- Risperdal Consta
- Zyprexa Relprevv
- Abilify Maintena
- Invega Sustenna (1 month), Invega Trinza (3 month)
Non-Pharmacologic Treatment

- Electroconvulsive Therapy
  - The combination of ECT with antipsychotics can increase the effectiveness of the medication.

- TMS
  - There is no definitive evidence that TMS is an effective additional treatment for negative symptoms, particularly in early stage schizophrenia.

- Cognitive Behavioral Therapy
  - Shows to be an effective option for the positive symptoms of psychosis.

- Social Skills Training
  - A 2013 study showed that 62% of patients receiving TMS plus ECT had achieved remission compared to only 46% in the medication-only group. 80% in the TMS group showed functional improvement compared to 75% in the medication-only group.

- Family Psychoeducation and Therapy
  - Caliper trials of families and aggress in family members advice widely accepted and recommended as key elements of a comprehensive treatment approach.

Source:


Treatment Resistance and Failure

- An adequate medication trial is defined as the maximum tolerated dose for 16 weeks.

- Considerations for treatment failure: smoking, drug interactions (Carbamazepine causes hypercatabolism), illegal substance use, take with or without food, time of day.

- Clozapine:
  - Superior choice for treatment refractory schizophrenia.
  - Guidelines for use: failure of 2 adequate antipsychotic trials.
  - Consider ECT.

Source:

Comorbidities

- Cardiovascular Risk Factors
- Substance Abuse
- Mood Disorders
- Schizophrenic patients are 40% less likely to receive treatment for medical comorbidities.

Source:
### Cardiovascular Risk

- More likely to have multiple risk factors and a higher chance of developing 3 or more risk factors
- Increased risk of diabetes
- 78% of people with schizophrenia smoke compared to 25% of population
- Physical inactivity is 3x greater
- CATIE Study: 43% of schizophrenia subjects had metabolic syndrome
- Antipsychotic medications also increase risk

### Substance Abuse

- More likely to have substance abuse
- A study including 1460 individuals with schizophrenia found that 60% use at least one substance of abuse and 37% had evidence of a substance abuse disorder
- Substance abuse is associated with increased psychotic symptoms, non-adherence to medication, and increased hospitalization
- “Self-medicate”

### Mood Disorders

- Increased prevalence of mood disorders
- As much as 57% suffer from comorbid depression
- A meta-analysis found 38% of schizophrenia patients present with at least one anxiety disorder
Questions?