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SERIOUS MENTAL ILLNESS
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Dementia Praecox - Saving the Brain!

Epidemiology of Schizophrenia

World prevalence	0.4% to ~1.9%
U.S. prevalence	0.8%
Sex ratio	~1:1
Age of onset	16 to 30 years, rare before puberty or after age 40 years
Life span	Shortened ~ 20 years

Neurobiology of Schizophrenia

DEMENTIA PRAECOX (1896)	SCHIZOPHRENIA (1906)
• Brain disease characterized by psychosis, brain atrophy, deteriorating course and early vegetative state	• Psychotic illness arising from severe psychological conflicts causing disruption of reality testing • Viewed as a functional fragmentation of personality rather than a biological brain disease

Schizophrenia: Nature vs. Nurture

DEMENTIA PRAECOX (1896)	SCHIZOPHRENIA (1906)
Genetics • Polygenic inheritance • 270 risk gene abnormalities (~1.35% of human genome • Strongly associated with cell migration, cell adhesion, cell alignment, cell differentiation, cell maturation, receptor structure, regulation of inflammatory processes, and neural network formation/maintenance • Schizophrenia risk is ~80% genetically determined, with an approximate 50% overlap with risk gene abnormalities for bipolar illness	**Environmental Risk Factors** = ~20% of risk variance Factors include: • Maternal infection during pregnancy (e.g., influenza) • Maternal stress during pregnancy, especially second trimester • In utero illicit drug exposure • Childhood adversity (e.g., abuse, deprivation, or neglect) • Being reared in an urban environment • Adolescent illicit drug exposure (e.g., cannabis or methamphetamine)
Genetic Abnormalities • Single nucleotide polymorphisms: 108 concentrated in the HLA complex, many of which are involved in regulation of inflammatory responses • Microdeletions and microduplications at 1q21.1, 2p16.3, 3q29, 15q13.3, and 16p11.2, as well as a large deletion on 22q11.21 and a microduplication on 16p11.2 • Sporadic translocations reported less well correlated with schizophrenia	**Role of Epigenetics** Environmental risk factors may alter brain development by: • Promoting or inhibiting gene expression via small peptides or ribonucleic acids (RNA). • Some epigenetic changes may be passed on to offspring. • Altering acetylation of histone, altering the winding and unwinding of DNA for copying. • Methylation of deoxyribonucleic acid (DNA) segments.

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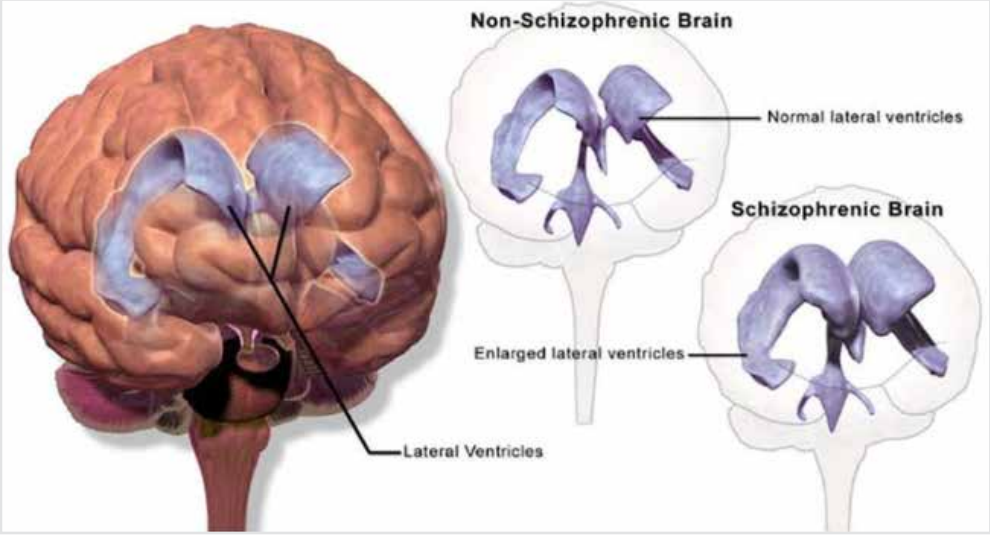
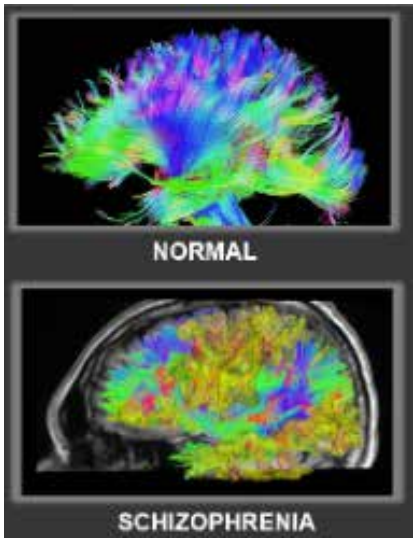
Phenotypic Course

In Utero	Abnormal neuroblast migration and misalignment
Childhood	Excessive loss of synaptic connections and neurons
Adolescence	Excessive pruning of synapses during frontal and temporal lobe maturation resulting in overt psychosis
Early psychosis	Accelerated loss of brain mass (~5% per year), worsened by undertreatment and number of psychotic relapses
Later psychosis	Ongoing cortical thinning and increased risk of neurocognitive disorder

Phenotypic Phenomena





Types of Schizophrenia

NON-RESISTANT (DOPAMINE-RESPONSIVE)	RESISTANT (DOPAMINE NON-RESPONSIVE)
• Characterized by increased/unstable dopamine signal transduction in the ventral tegmentum • May be improved by dopamine antagonist, dopamine partial agonist, and muscarinic antipsychotics (i.e., by reduction in increased dopamine signal transduction resulting in reduction of positive symptoms)	• Dopamine signaling in the ventral tegmentum may be largely normal, with psychosis resulting more from deficits in frontal glutamate transduction and increased 5HT-2A serotonin signal transduction (i.e., effect similar to psychomimetic drugs such as phencyclidine or lysergic acid diethylamide-25, respectively • Much greater probability of response to clozapine (i.e., 40% to 60% v. < 7%)

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Adequate Antipsychotic Trial for Schizophrenia Spectrum Psychosis

- Best for longstanding symptom improvement
    - Long-acting injectable (LAIs) → better outcomes and lower rehospitalization rates

Monitoring via plasma concentration (whether LAI or oral)

1. Initiate the antipsychotic and achieve **minimum response threshold**.
2. If problematic behaviors/symptoms persist, consider increasing dose to mid-level plasma concentration.
3. If problematic behaviors improved, **wait 2 weeks** to find if more than 20% improvement, if not…
4. Increase plasma concentration, as symptoms dictate, to **point of futility** before considering another medication.
5. Stop titration if **dose-limiting side effects** or **persisting substantial improvement**.

If 2 adequate antipsychotic trials don't work:

- The patient is dopamine non-responsive and has *treatment-resistant schizophrenia* (TRS).
    - ***CLOZAPINE*** is the gold standard.

Take Home Points

- ✓ Schizophrenia **progression** is **promoted by periods of undertreatment and the number of psychotic exacerbation episodes**.
- ✓ Schizophrenia presents in **dopamine-responsive and dopamine-nonresponsive forms** (treatment-resistant schizophrenia), with **clozapine** being the only viable pharmacological treatment in the large majority of cases.
- ✓ Structured medication trials that achieve the **minimum response threshold** and then titrate, using the **2-week rule**, to end-points of **treatment response, intolerable side effects, or the point of futility** as guided by plasma concentrations offer the highest probability of effective treatment.
- ✓ **Clozapine** remains the **"gold standard"** for **treatment resistant schizophrenia**.

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