Schizophrenia

Learning Objectives

- Define and describe psychosis
- Understand and describe the symptoms and diagnostic criteria for schizophrenia
- Describe and discuss the hypothesized causes of schizophrenia
  - Acknowledge and evaluate the limitations of each one
- Discuss available treatments for schizophrenia, including their mechanism of action and side-effects

Psychoses are a group of psychological disorders in which patients experience **a loss of contact with reality**

- *From the greek for*
  - *"psyche"* – mind/soul
  - *"-osis"* – abnormal condition

Self-portrait by an individual with schizophrenia

Schizophrenia is a psychotic disorder (probably a group of disorders) which produces disturbances in:

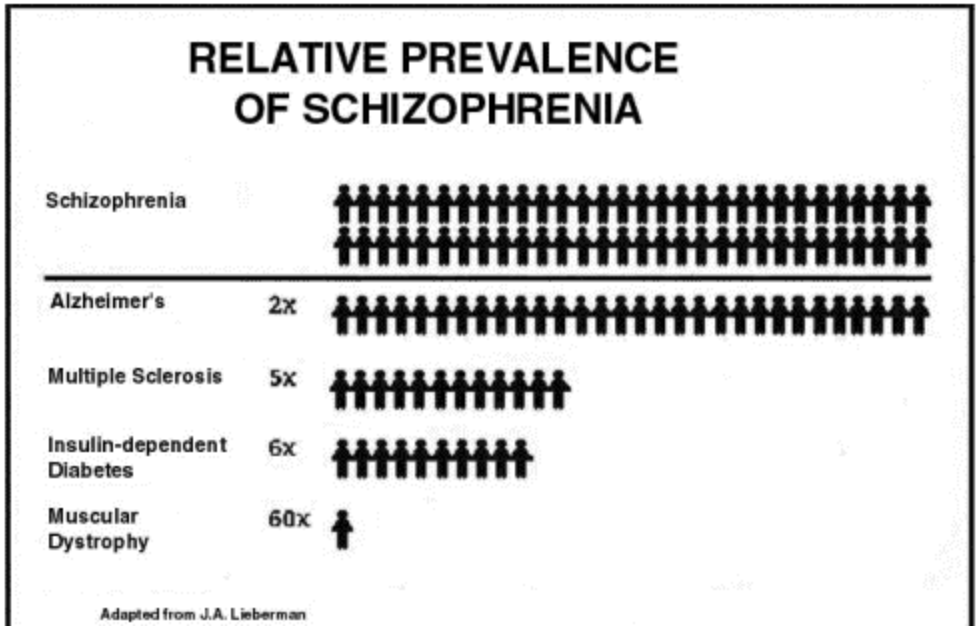
- → perception of reality
- → cognition
- → interpersonal relations
- → mood
- → social integration

Prevalence and Impact

Common and most debilitating psychiatric disorder.

- Affects 1 in 100 people (~300 000 Canadians)
  - Highly comorbid with depression, anxiety and/or substance abuse
  - 70-80% of affected individuals are unemployed

Cost of care is staggering at ~$5 billion per year.



History

- The condition historically known simply as "madness" or "lunacy" likely corresponds to what we now call **schizophrenia**

- **Emil Kraeplin** (1856-1926) was the first to thoroughly define the symptoms of schizophrenia
  - He called it ***dementia praecox*** – "premature dementia *(L.)*" based on its progressive nature and appearance in late adolescence.

- **Eugen Bleuler** (1857-1939) recognized that this was not premature aging and coined the term **schizophrenia**
  - **Schizophrenia** means "*split mind*" *(G.)*
    - That is to say that different component of the individual's mind become disconnected from each other and reality in general
  - This reference to a split mind has lead to the common misconception that it is the same this a dissociative identity disorder or 'spilt personality disorder'

Emil Kraeplin (above) and Eugen Bleuer (below)

Signs and Symptoms

As a group of disorders, signs and symptoms can vary significantly between affected individuals.

They do however fall into 3 main categories:

1) **Positive** – behavioural excess or symptoms not experienced by non-affected individuals

   i.e. - delusions and hallucinations

2) **Negative** – behavioural deficits or impairments

   i.e. – apathy and anhedonia

3) **Disorganized** – erratic changes in speech, motor behavior, and emotions

I DON'T **FEEL,**
and neither do I care to.

-Apathy

* Note positive and negative do not refer to the relative, subjective value/impact of the symptoms *

Positive Symptoms

Delusions are strongly held beliefs despite overwhelming evidence to the contrary

Delusions can be:

Bizarre or clearly implausible and not understandable

e.g. - a belief that all of your internal organs have been switched with someone else's without leaving a scar

Non-bizarre which although false are at least possible

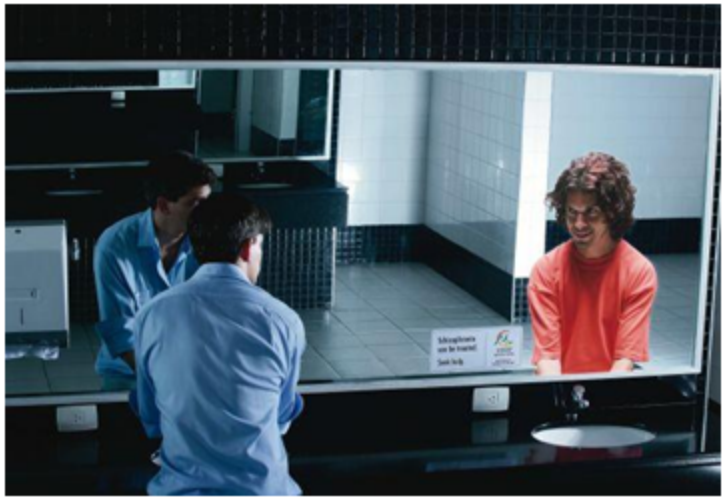
e.g. – a belief that you are under constant police surveillance

The most common type of delusions in schizophrenia are **persecutory delusions.**

- Generally a belief that the individual is being unfairly targeted , followed, harassed, cheated, drugged, conspired against, spied on, attacked, or otherwise obstructed in the pursuit of his or her goals

Positive Symptoms

Hallucinations are perception in the absence of an actual sensory stimulus. Hallucinations may affect any of the senses.



Auditory hallucinations or "hearing voices" that are not ones own are most common in schizophrenia

Command hallucinations occur in the form of instructions to the individual.

- While they may be innocuous, they may also include **commands to cause harm** to one's self or others

Interesting note – recovery is more common in societies where 'hearing voices' may be interpreted positively (i.e. - your ancestors speaking to you) or at least not considered to be you .

Negative Symptoms – the "A's"

Apathy or avolition: inability or lack of desire to "get started"

- Leads to emotional and social withdrawal
- Also leads to difficulty in performing basic day-to-day functions
  - i.e. - problems with hygiene, keeping a job, and keeping a place to live

Autism: refers to the tendency to keep to oneself and lose interest in other people or the surroundings.

- **Note: '*autism*' here refers to a set of behaviors, not comorbidity with *autism* the disorder.**

Anhedonia: *"without pleasure (G.)"* the inability to enjoy or general indifference towards activities that are typically considered to be pleasurable

Affect flattening: overall reduction in the range and intensity of emotional expression

Disorganized Symptoms

Cognitive difficulties

Difficulties planning, focusing and/or learning

Disorganized speech – Severe enough to substantially impair effective communication

- Loosely associated or incoherent speech (sometimes referred to as word salad)
- Individuals flip between subjects and head off on a tangent frequently
- Some individuals may alternatively suffer from a poverty of speech **(alogia)**

Inappropriate affect - in addition to flattened affect, schizophrenics may display emotions that are inappropriate for the current situation

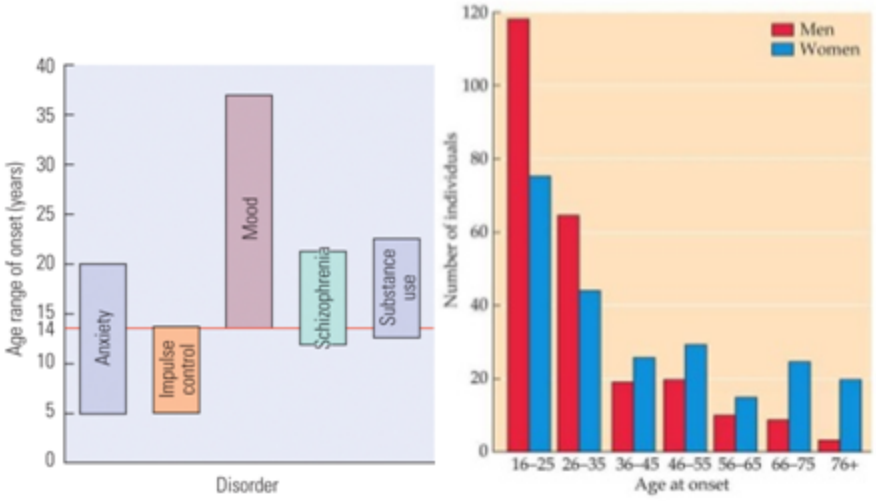
- e.x. – laughing at a funeral, or overall silliness in a serious setting

Motoric changes ranging from unpredictable movement and agitation to catatonic immobility

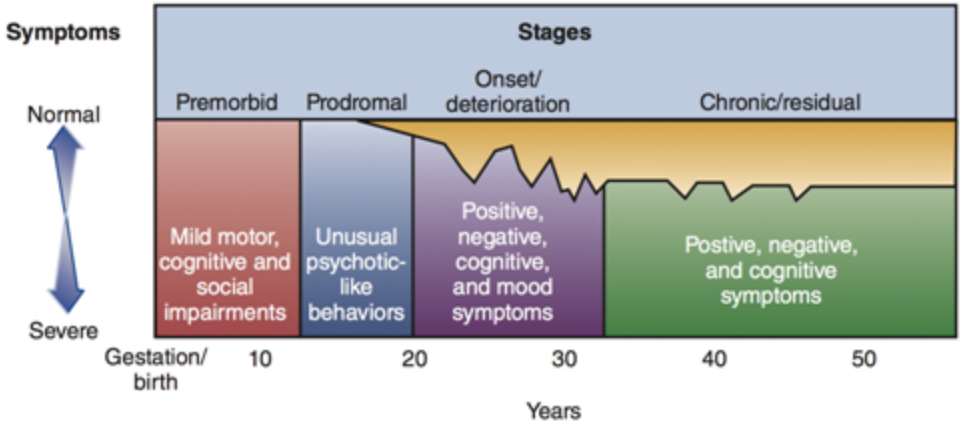
- **Catatonic behaviors** may be any of the following:
  - a decrease in reaction to the surrounding environment
  - general motionless and apparent unawareness
    - rigid or bizarre postures, may be 'poseable'

Disease Onset

- Generally occurs in **young adulthood (20's)**
  - Males earlier than females
- Occurs at a time when individuals are entering the adult world and becoming fully independent
  - Disruption to the process of establishing one's place in society has life long social implications (lack of education →lack of employability → social isolation ...)
- Disease usually begins with 1-2 years of lower grade symptoms, generally characterized by marked mood and behavioural changes
- Diagnosis usually occurs with the first appearance of psychotic symptoms (delusions and/or hallucinations) known as a **psychotic break**



Average age of disease onset in comparison with other psychiatric disorders and by sex.



Pattern of schizophrenic symptoms across the life span.

A video…

http://www.youtube.com/watch?v=gGn18dqEoPQ

Updating the DSM

- Historically schizophrenia was separated into 5 subtypes:
  - Paranoid
  - Disorganized
  - Catatonic
  - Undifferentiated
  - Residual types

- These classifications were eliminated in the DSM5

WHY?

  - They held little diagnostic value, low reliability, and poor validity.
  - They did not predict patterns of disease progress or therapeutic potential.

Diagnosis According to the DSM5

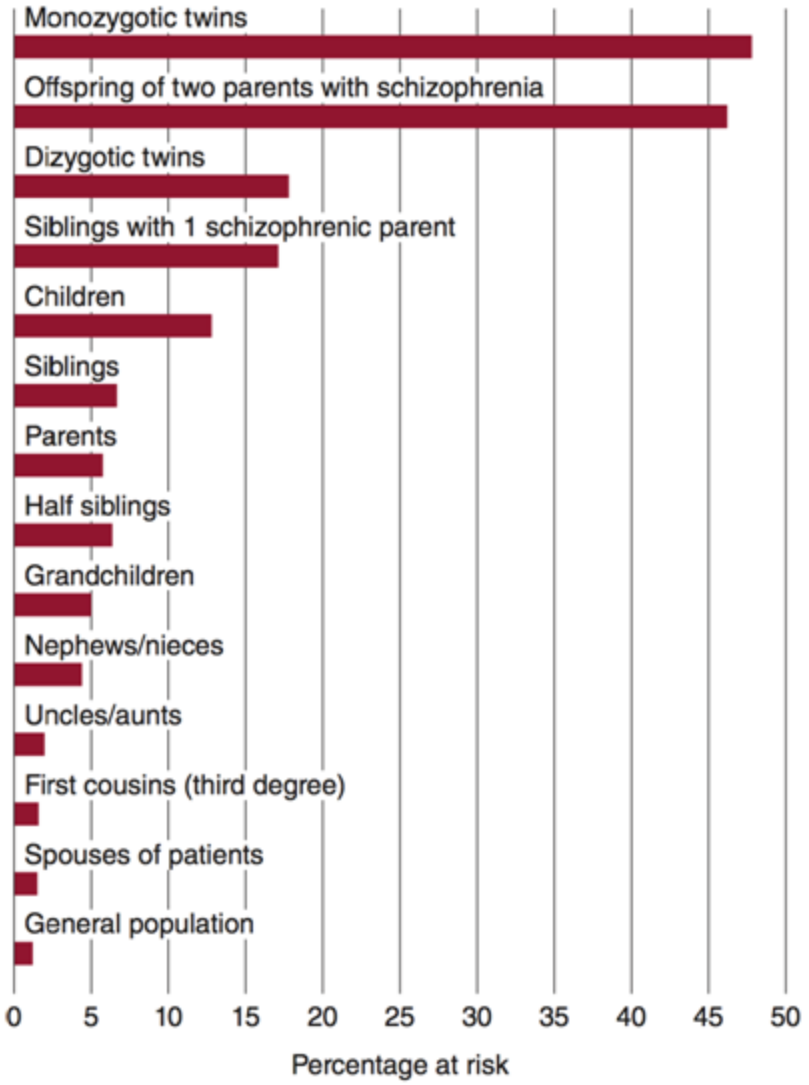
The DSM lists **5 diagnostic symptoms**:

1) Delusions
2) Hallucinations
3) Disorganized speech
4) Disorganized or catatonic behavior
5) Negative symptoms (i.e – blunted emotion, anhedonia, avolition)

- Signs must persist for a minimum of 6 months; including at least 1 month consecutive
- Must show at least one of the first 3 symptoms
- Must rule out:
  1. mood disorder
  2. substance abuse
  3. other medical conditions (particularly developmental disorders, i.e. – autism)

Etiology - Genetics

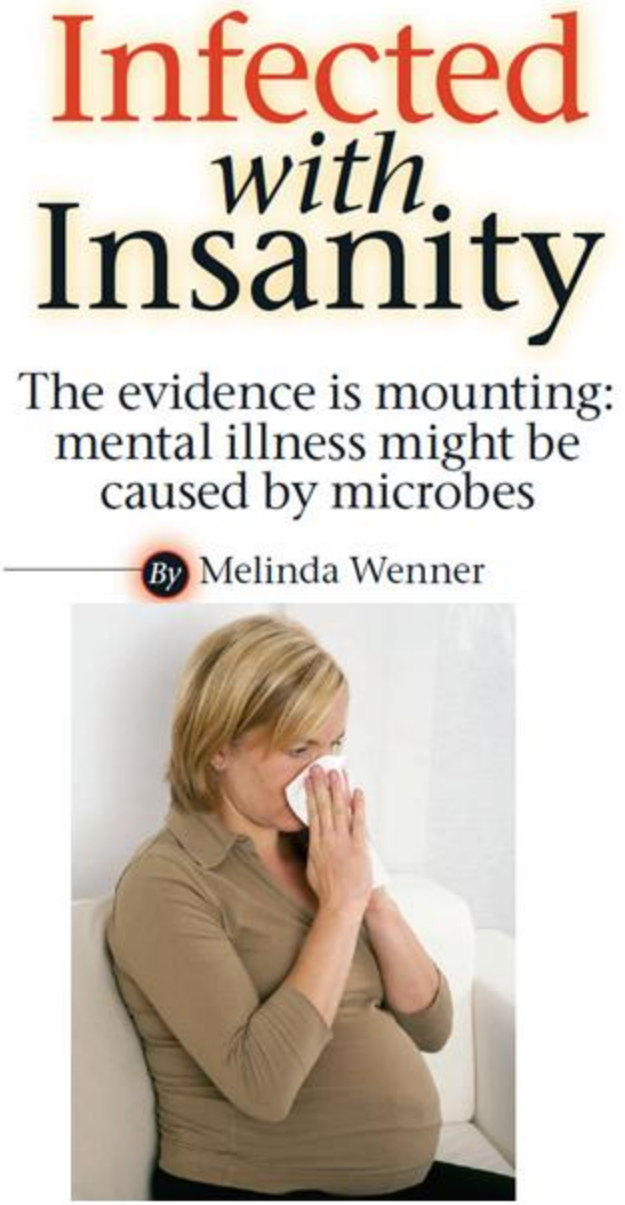
- Genes play an important role is predicting disease
  - **Amount of DNA shared with an affected family member is directly related to risk of developing the schizophrenia**
- No single gene or mutation had been identified
- Genes alone may not be the only factor
  - There is strong evidence for environmental impact on gene expression (**epigenetics**)



Etiology - Development

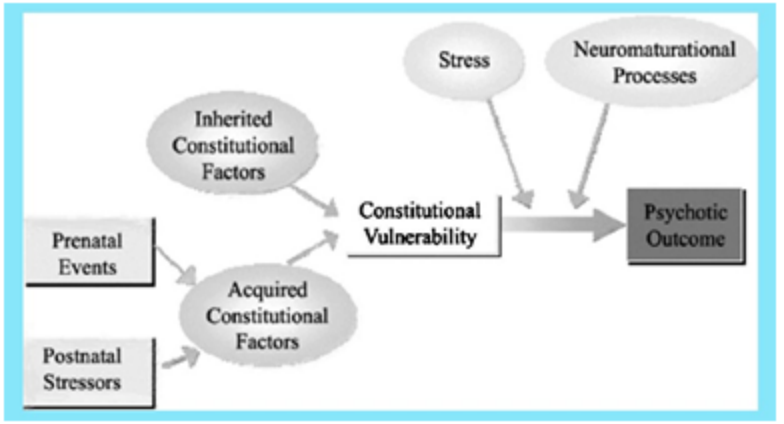
- There is evidence that **adverse events during the perinatal period** (during gestation or immediately after birth) increase an individual's risk of developing schizophrenia

  - hypoxia, infection, stress and/or malnutrition are all associated with increased risk
    - These may arise due to:
      - Maternal infection during pregnancy
      - Injury during labour and delivery



Etiology - Stress

- **Stress** seems to be a contributing factor in regards to:
  - **Overall risk of developing schizophrenia**
    - Stressors which affect susceptibility are diverse:
      - childhood trauma and abuse
      - death of a parent
      - being bullied
      - social adversity
      - family dysfunction
      - unemployment .....

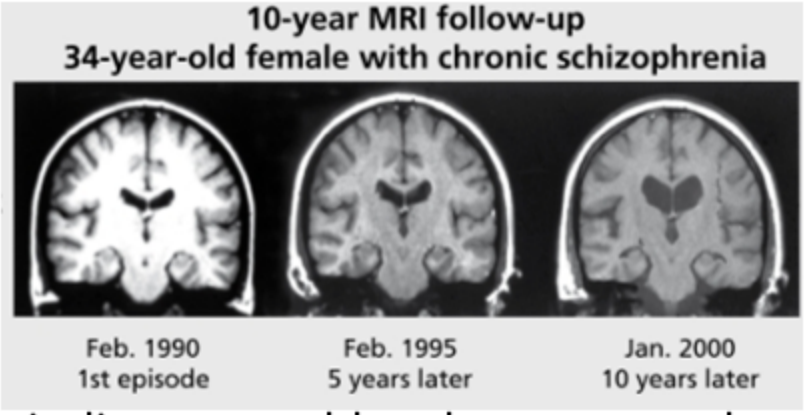


  - and as **a precipitating factor** in those who are susceptible:
    - The initial **psychotic break** leading to diagnosis is almost always preceded by a stressful life event

Neuroanatomical Changes – Structural

The most consistent neuroanatomical findings in schizophrenia are a **reduction in brain weight** and an **enlargement of the ventricles**

- It is unclear if this change causes schizophrenia or is produced by the disease
- The extent of these changes correlate with length of the disease
  - This suggests that there is a neurodegenerative component of to schizophrenia



1. ENLARGED VENTRICLES

Enlarged ventricles in and of themselves do not indicate a problem but suggest that there **is a change in the cellular make up of the brain** which is being replaced by **CSF**

2. REDUCED BRAIN WEIGHT

Specific neuroanatomical changes may be correlated with symptoms:

a) Decreased frontal and temporal lobe volume
   - cognitive deficits

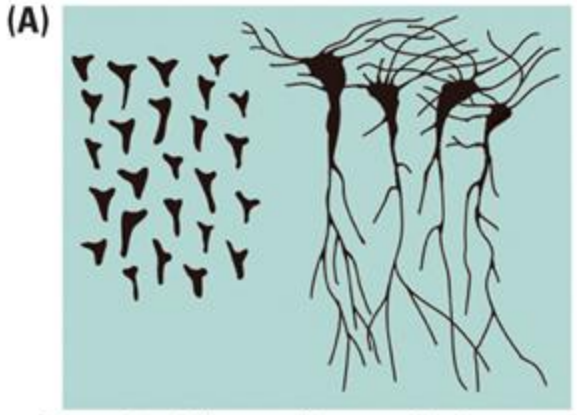
b) Reduced volume of the basal ganglia
   - reduced emotional control and motoric changes

c) Reduced hippocampal volume
   - learning and memory deficits

Neuroanatomical Changes- Cellular

Postmortem studies actually reveal **abnormal cellular organization**

- This suggests a developmental origin for the disease and that the symptomatic disorganization seen may actually reflect at literal neuroanatomical disorganization



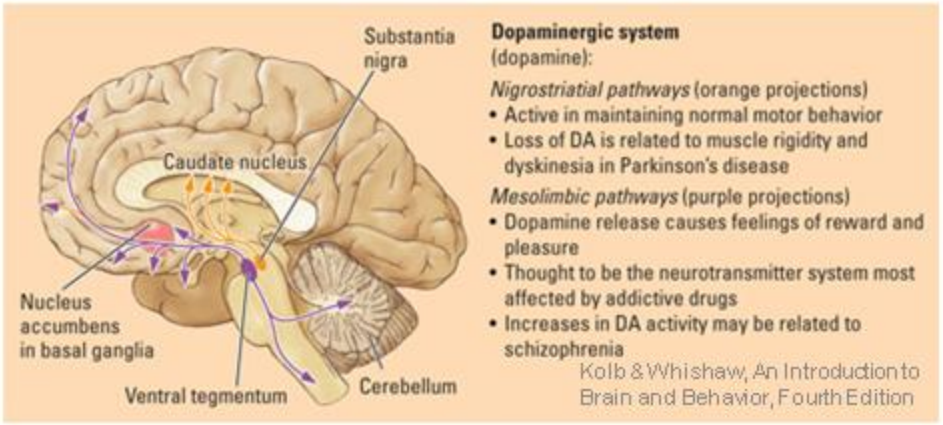
Organized (normal) pyramidal neurons

Disorganized (schizophrenic) pyramidal neurons

Neurochemical Correlates - dopamine

Dopamine Hypothesis of Schizophrenia

– Proposes that schizophrenia symptoms are due to excess activity of the neurotransmitter dopamine

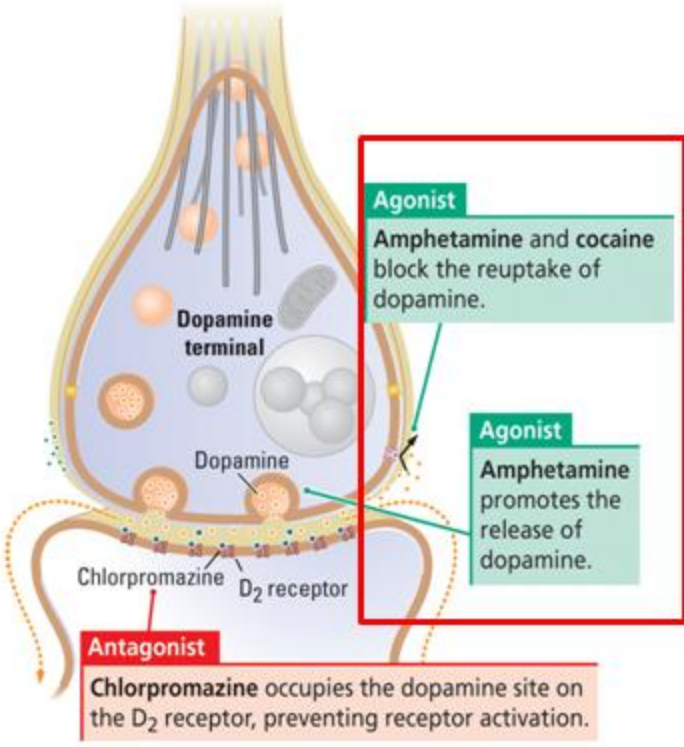


Evidence

- Antipsychotic drugs block D_2 receptors
- Amphetamine use promotes release of dopamine and can also produce symptoms similar to schizophrenia

Problem

- Conventional antipsychotics are only partially effective in most affected individuals, and ~30% of patients show no improvement
- Most postmortem studies have failed to identify specific dopaminergic changes in the brain of schizophrenic patients



Neurochemical Correlates Cont'd

Serotonin Hypothesis of Schizophrenia

- Proposes that schizophrenia symptoms are due to increased activity of the neurotransmitter serotonin

Evidence

- LSD binding of to 5-HT2 receptors, mimics serotonin and can produce hallucinations similar to schizophrenia
- Atypical antipsychotic drugs block 5-HT_2 receptors
- Substantial changes in the serotonergic systems have been identified in the schizophrenic brain

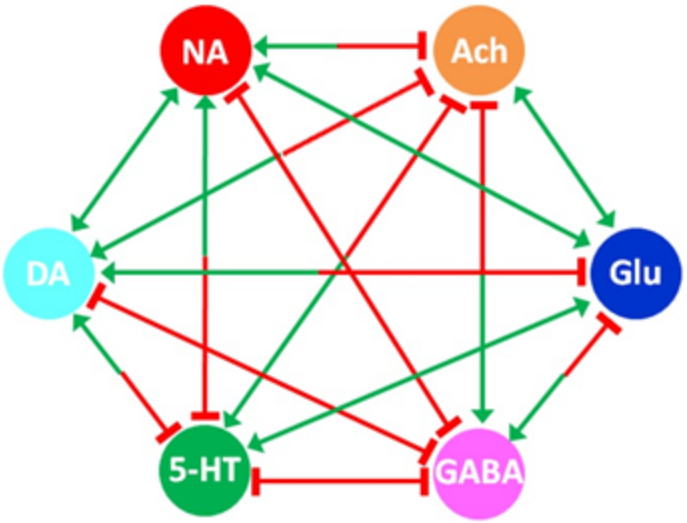
Problem

- Lead to predominantly visual hallucination, not the more common auditory hallucinations of schizophrenia
- None of the cognitive deficits of schizophrenia are induced with LSD

Other neurotransmitters

- Glutamate over activity?
  - PCP (angel dust) and ketamine (Special K), which are glutamate receptor antagonists, induce schizophrenia-like symptoms (both positive and negative) in normal individuals and worsen symptoms in affected individuals
  - Evidence for reduced NMDA receptor function in the schizophrenic brain
- GABA reductions?
  - GABA concentrations are reduced in individuals with schizophrenia, likely contributing to confusion and irritability

- While each of these theories are unable to explain the disorder 100%, that **does not** mean that they are incorrect
  - We know that all of the neurotransmitter systems regulate one another, **so it is entirely possible they are all correct**



- Given the diverse set of symptoms experienced by each individual, each one of these theories may have a greater or lesser role in their specific manifestation of the disease

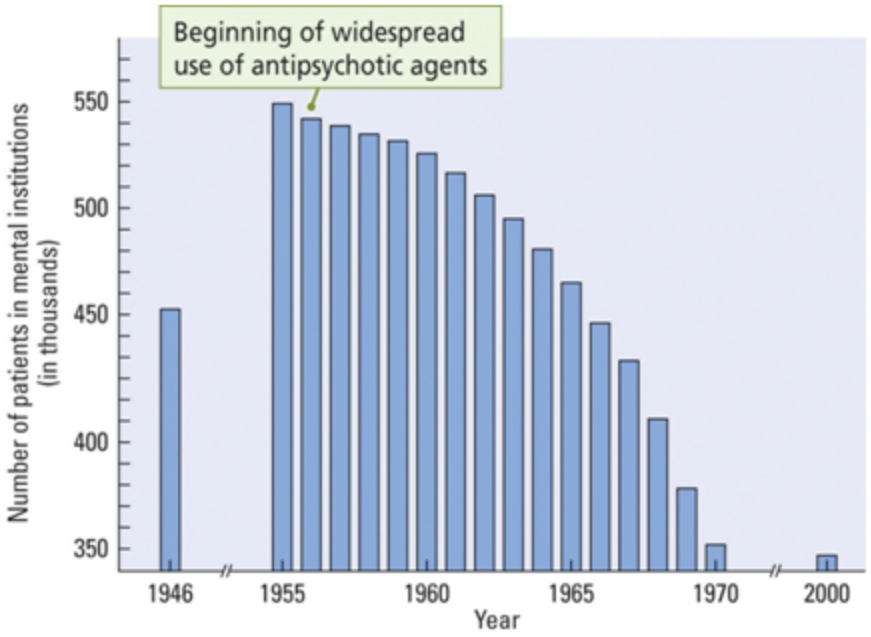
Pharmacological Therapy

- *Since* schizophrenia is classified as a psychosis, drugs used to treat it as known as **antipsychotic agents**

- **Early treatment** is key:
  - Allowing for less psychosocial disruption
  - Prevent degenerative brain changes which will likely exacerbate symptoms and worsen disease course

- Antipsychotic treatment is most effective at **managing positive symptoms** of the disease

- Since their use began in the 1950's, antipsychotic drugs have significantly reduced the number of institutionalized patients



Kolb & Whishaw, An Introduction to Brain and Behavior, Fourth Edition - Chapter 6

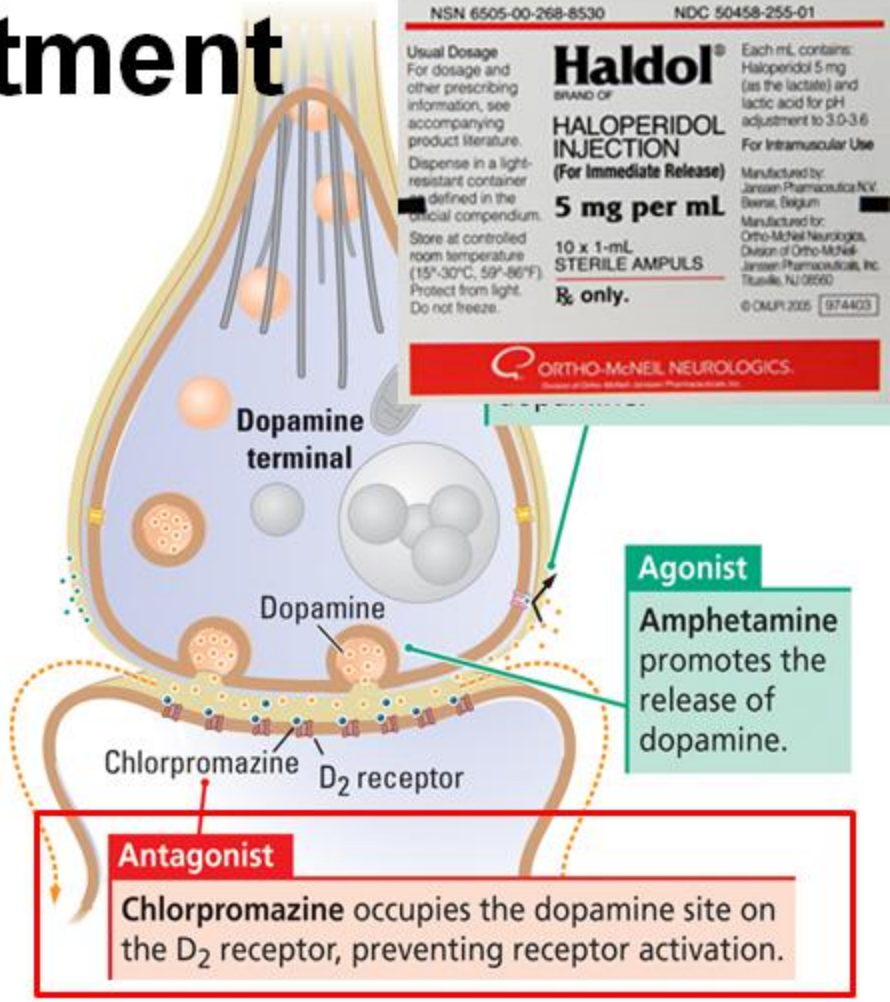
Antipsychotic Treatment

Administered since the 1950's, **conventional antipsychotics,** such as haldol, improve predominantly the positive symptoms of the disease.

Mechanism of action - block the dopamine D_2 receptor

Administered since the 1990's, **atypical antipsychotics**, such as seroquel, improve both the positive and negative symptoms of the disease.

Mechanism of action - Weakly block D_2 receptors but also block serotonin 5-HT_2 receptors



Side Effects of Antipsychotics

Many patient on antipsychotics medications report experiencing side effects.

The most troublesome side effects are:

Hyperprolactinemia

- dopamine normally inhibits release of prolactin, inhibition of this system by antipsychotic drugs leads to breast development and milk production

Extrapyramidal symptoms

- continuous muscle spasms, motoric restlessness, rigidity, **tardive dyskinesia (TD)**
  - TD is involuntary movement reminiscent of Parkinson's disease, ***often permanent***

Neuroleptic malignant syndrome

- muscle stiffness, difficulty breathing, altered mental status, renal failure, fluctuations in blood pressure, tremors, dehydration, racing heartbeat, and very high fever, ***can be fatal***

Atypical antipsychotics generally have a more favorable side effect profile

- risk of tardive dyskinesia and neuroleptic malignant syndrome is greatly reduced
- they have an increased incidence of metabolic side effects (weight gain and type II diabetes)

Compliance with treatment is a major issue with this disorder.

WHY?

.... in part due to the nature of the disease:

- Distrust of the medical establishment
- Lack insight into their illness means that they do not see the need for medication or other mental health help

....in part due to the side effects of the medications:

- Extrapyramidal symptoms are very difficult to live with
- Also due to inhibition of reward pathways in the brain it is difficult for patients to feel good

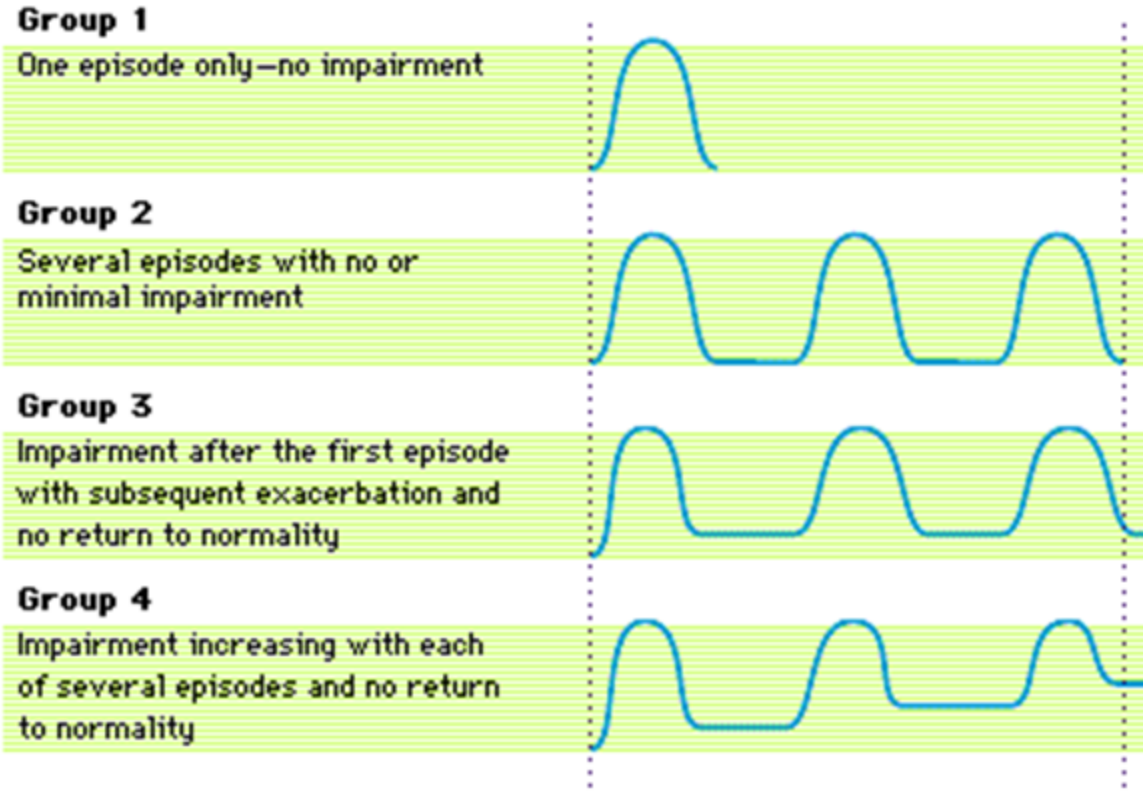
Estimates are that 40-60% of patients quit their medication within a year.

- Full range of symptoms can return within a week
- Discontinuation of treatment greatly increases the risk of hospitalization and suicide

Course of Disease Progression

- Psychotic episodes may last weeks or months

- The periods between episodes vary significantly from full remission to a continuously worsening baseline



Life with Schizophrenia

Despite improvements in therapy, current evidence suggests that many affected individuals **do not get help** and end up struggling among the world's homeless population.

Of those we can track, this is the long term picture of life with schizophrenia,

10 years after diagnosis:

- 25% have experienced recovery
- 25% are much improved and living independently
- 25% are improved but still require a constant support system
- 15% end up hospitalized
- 10% are dead (most commonly due to suicide)

30 years after diagnosis:

- 25% of people are in some form of recovery
- 35 % of people are improved and lead fairly independent lives
- 15% need of extensive assistance
- 10% are hospitalized
- 15% are dead

* NOTE that recovery ≠ remission but rather the ability to successfully manage symptoms which contributes to an ability to lead a fulfilling and meaningful life.

A Social Salve for Schizophrenia

Treating the less well-recognized social aspects of schizophrenia could help patients lead fuller, more productive lives

By Matthew M. Kurtz Illustrations by Patrick George

Most of us in the field of schizophrenia have met people who function just fine in social settings as long as no one mentions the CIA.