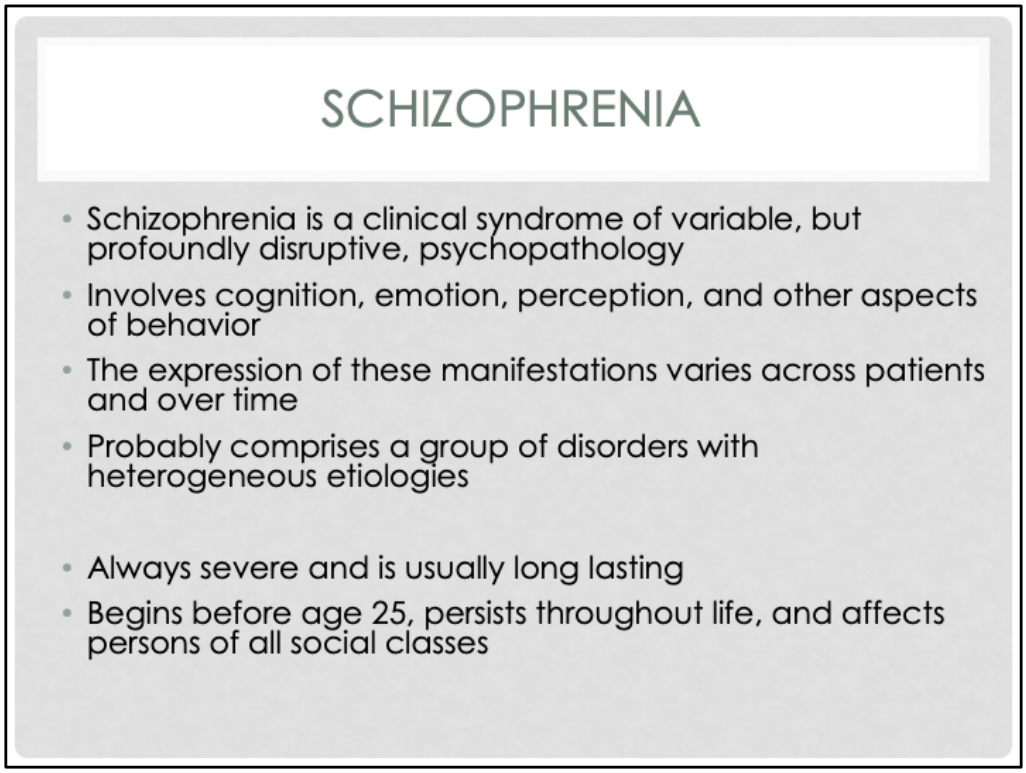
CLINICAL ASPECTS OF SCHIZOPHRENIA

ROBERT HEROLD



Schizophrenia is a clinical syndrome of variable, but *profoundly disruptive*, psychopathology **– not able to maintain their earlier level of functionality.**

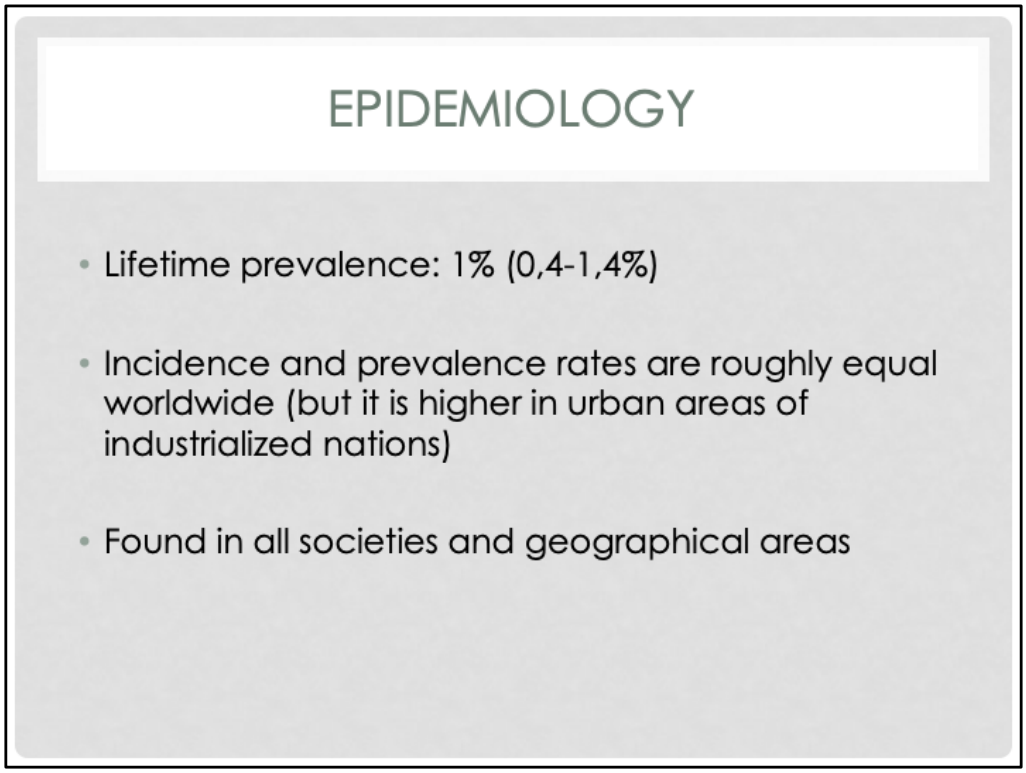
Nearly the whole personality is affected – it involves cognition, emotion, perception, and other aspects of behavior

The expression of these *manifestations varies* across patients and over time.

However this great variability suggests that sch probably comprises a group of disorders with *heterogeneous etiologies*

Schizophrenia is Always severe and is usually long lasting **- Schizophrenia is among the top 10 disorders causing disability.**

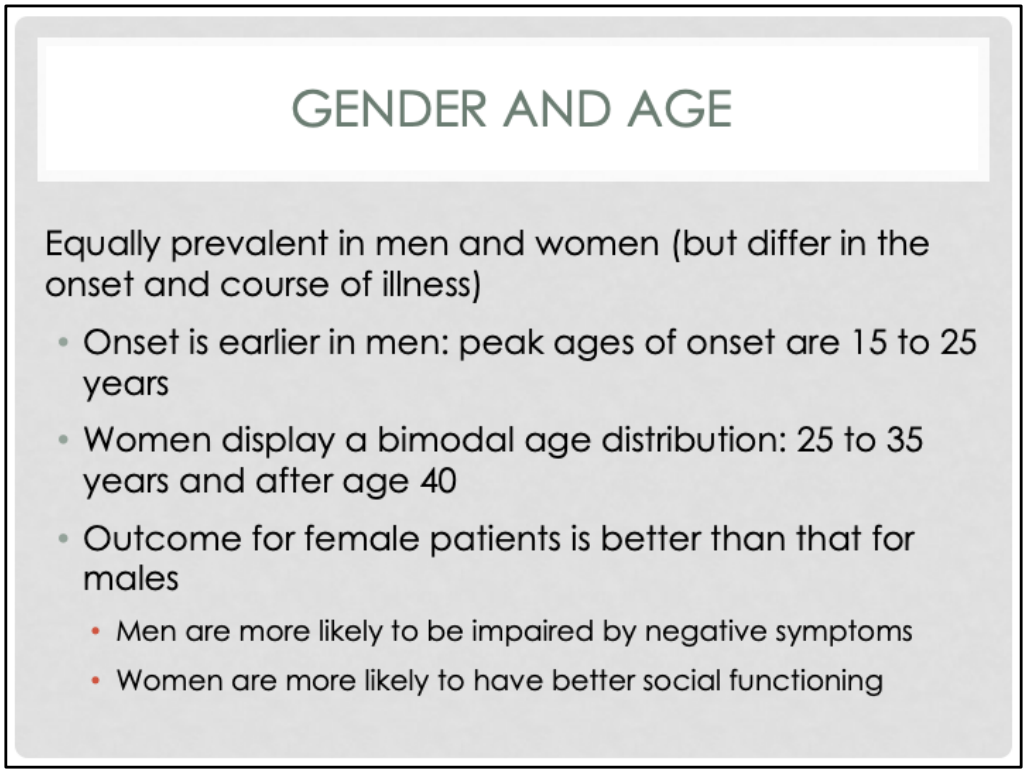
It begins before age 25, *persists throughout life*, and affects persons of all social classes – **and so it affects the most productive years of a certain peopl**e.



Lifetime prevalence: 1% (0,4-1,4%) – **which means that about 1 person in 100 will develop schizophrenia during their lifetime.**

Incidence and prevalence rates are roughly equal worldwide, **however there are slight differences in distribution** (it is higher **for persons born** in urban areas of industrialized nations) - **These observations suggest that social stressors in urban settings may affect the development of schizophrenia in persons at risk.**

SCH is found in all societies and geographical areas **independent of the given cultural background**. **Some researchers suggest that sch is present from the birth of human culture, and this is the price we pay for language (which is linked to brain lateralization and asymmetry). The development of high level cognitive functioning in human beings also increase the vulnerability to schizophrenia. According to Crow schizophrenia is the result of the loss of normal asymmetry.**



Equally prevalent in men and women **(however the two gender** differ in the onset and course of illness)

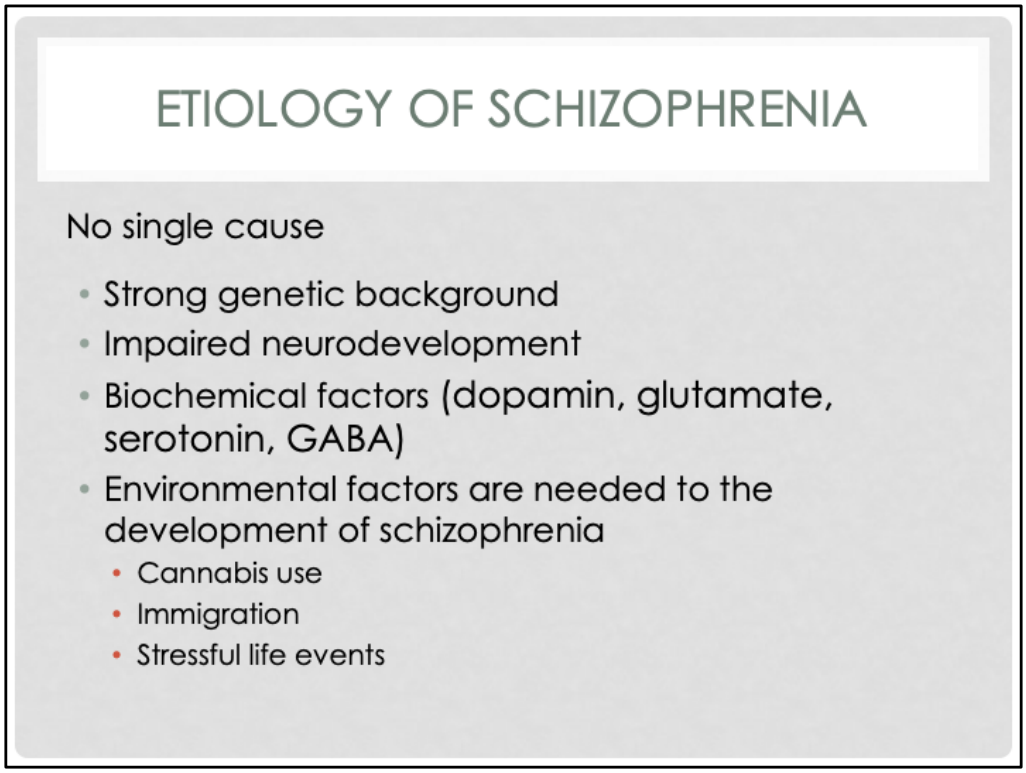
Onset is earlier in men: peak ages of onset are 15 to 25 years (**the earlier is the onset the worse is the outcome: childhood onset sch, which is rare, has the worst outcome)**

Women display a bimodal age distribution: 25 to 35 years, and **unlike men, women display a second peak occurring in middle age. Approximately 3 to 10 percent of women with schizophrenia present with disease onset after age 40.**

Outcome for female patients is **somewhat** better than that for males

Men are more likely to be impaired by negative symptoms**, and they exhibit more deficits symptoms**

In contrast, Women are more likely to have better social functioning, and **less cognitive symptoms.**



No single cause

Genetic studies revealed a Strong genetic background

In the case of monozygotic twins (prevalence 47%) who have identical genetic endowment, there is an approximately 50 percent concordance rate for schizophrenia. This rate is four to five times the concordance rate in dizygotic twins (12%) or the rate of occurrence found in other first-degree relatives (i.e., siblings 8%, parents, or offspring). The likelihood of a person having schizophrenia is correlated with the closeness of the relationship to an affected relative.

Chromosomal sites: 1q, 5q, 6p, 6q, 8p, 10p, 13q, 15q, 22q

DISC 1, *COMT*, *NRG 1* genes

Genetic studies suggest that genes involved in neurodevelopment and brain plasticity are affected in sch, and the result is an impaired neurodevelopment.

Biochemical factors (dopamine, serotonin, glutamate, GABA):

Neurotransmission is also impaired in sch. Dopamine dysfunction is still the most prominent hypothesis behind the symptoms of sch, but glu, ser, and GABA are also affected in sch.

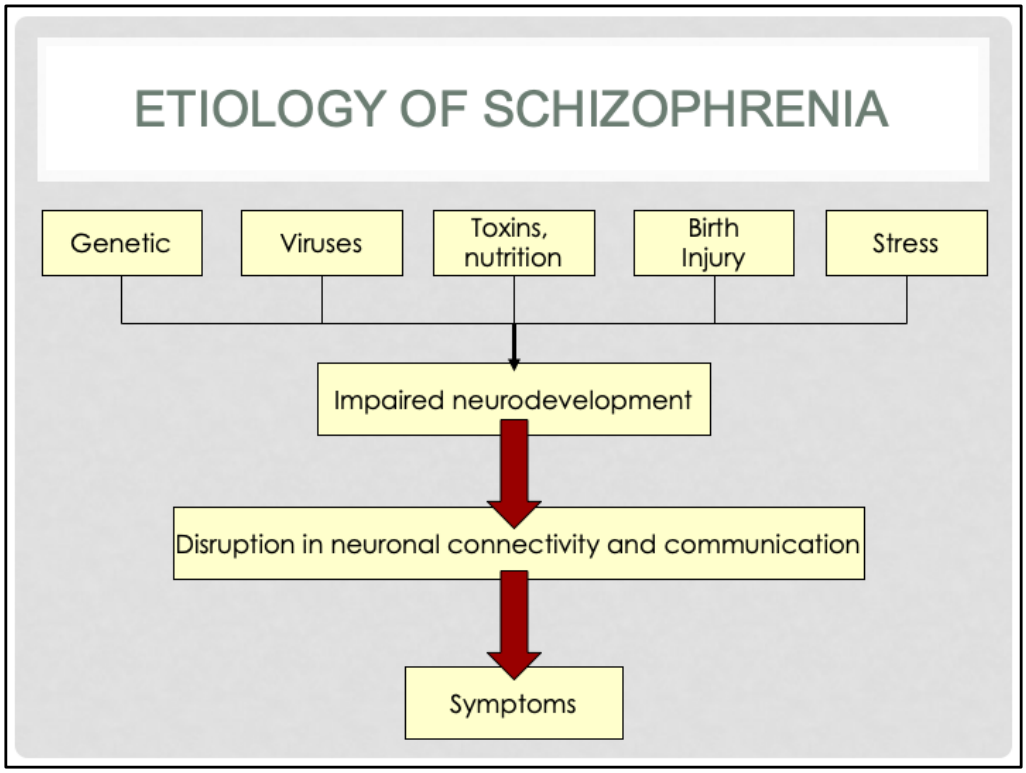
However beside genetic and biological factors, environmental factors are **also** needed to the development of schizophrenia.

Such environmental factors are:

Cannabis use **shows the strongest association with sch. It impairs the synchronization of the activity of different brain areas.**

Immigration **(getting into foreign cultural settings increases the risk to develop sch)**

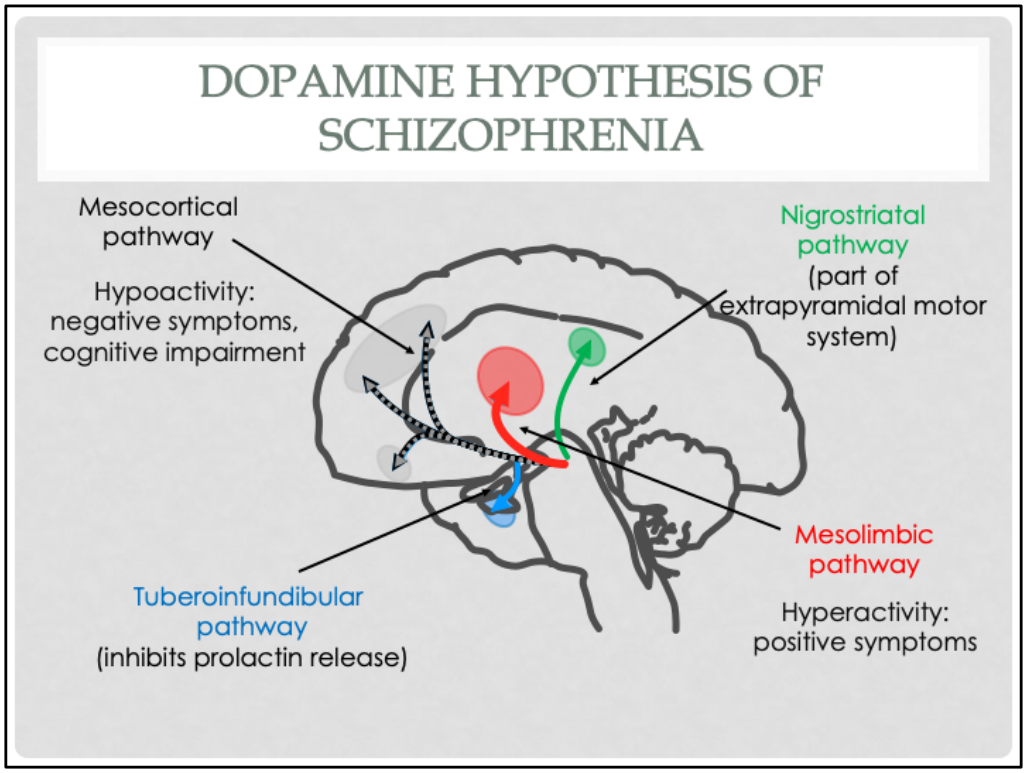
And Stressful life **events may also play role in development of sch in patients at risk. It is common before the onset of sch.**



Here you can see the simplified neurodevelopmental hypothesis of sch. According to this several factors, such as genetic factors, virus infection or toxins and nutrition during the pregnancy, birth injury and perinatal stress may lead to an impaired neurodevelopment.

These etiological factors affect the formation and migration of neurons, the synaptogenesis, programmed cell death (pruning and apoptosis). Which in turn leads to an anatomical and functional disruption in neuronal connectivity and communication.

This miswiring results in symptoms in the early adulthood, when certain brain maturational processes are terminated, e.g. the maturation of prefrontal cortex.



There are 4 major dopamin pathways…
Two of them are affected in schizophrenia – mesocortical and mesolimbic.
Mesocortical pathway is hypoactive, which means that there is too little dopamin in the synapses. This hypoactivity is responsible for the cognitive and negative sympotms.
Mesolimbic pathway is hyperactive, which means that too much dopamin is in the synapses. This hyperactivity is responsible for the positive symptoms.

Hyperactivity is treated by D2 receptor blockers, namely by the antipsychotics. It imporves the positive symptoms, However It also causes side effects in the unaffected pathways. The D2 receptor blockade also affects the nigrostriatal and tuberoinfundibular pathways. D2 receptor blockade in NS pathway result in EPS, and the D2 receptor blockade in TI is responsible for the hyperprolactinemia.

According to the revised dopamine hypothesis, schizophrenia is characterized by too much dopamine in subcortical regions and too little in cortical ones.

- The predominant hypothesis regarding the pathophysiology of schizophrenia is that it is associated with impaired dopamine neurotransmission.[1,2] Four main dopaminergic pathways have been described:[3]
    - The mesolimbic pathway originates from the midbrain ventral tegmental area and innervates many components of the limbic system (ventral striatum/nucleus accumbens, parts of the amygdala and hippocampus, as well as phylogenetically old parts of the cortex)

Excess dopamine is associated with positive symptoms
D_2 receptor blockade in this pathway can help reduce positive symptoms

    - The mesocortical pathway also originates from the midbrain ventral tegmental area and innervates the neocortex, most densely the prefrontal cortex

Deficits in dopamine are associated with negative and cognitive symptoms
The mesocortical pathway is rich in 5-HT_{2A} receptors
Serotonin receptor antagonists increase dopamine levels and alleviate negative and cognitive symptoms

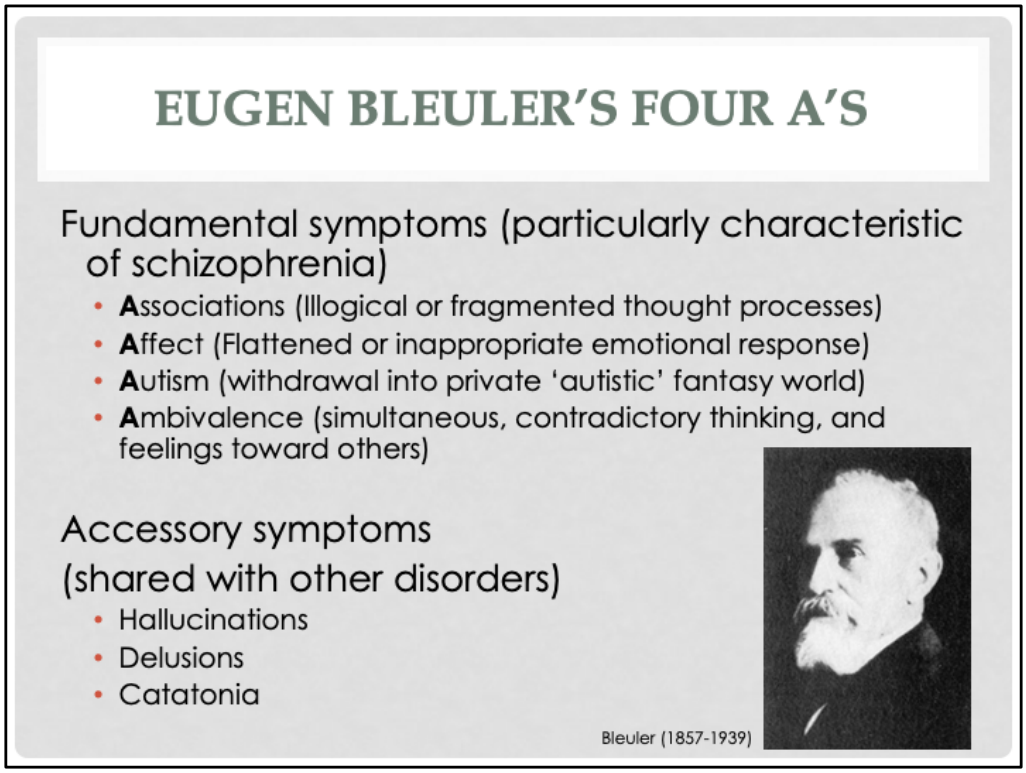
    - The nigrostriatal pathway has its origin in substantia nigra and projects to the putamen and caudate nucleus

Forms part of the extrapyramidal system and mediates
motor control
Dopamine receptor antagonism causes movement disorders such as EPS
5-HT_{2A} antagonists disinhibit dopamine release, and may
alleviate EPS

    - The tuberoinfundibular pathway originates in the cell bodies of the arcuate nucleus of the hypothalamus and projects to the portal vessels of the pituitary stalk. This pathway exerts tonic inhibition of the prolactin secretion from the anterior pituitary gland

Dopamine activity inhibits prolactin release, whereas serotonin stimulates its release
Blockade of D_2 receptors increases prolactin release and may cause sexual side effects
Balancing dopamine and 5-HT_{2A} antagonism is critical

    - Overactivity of the mesolimbic pathway has been implicated in development of positive symptoms of schizophrenia. The negative and some cognitive symptoms of schizophrenia have been associated with a reduction of dopamine activity in the mesocortical pathways[3]



Next topic is the symptoms of sch. First we should mention E. Bleuler. Bleuler recognized the diversity of symptoms in sch, and he tried to grasp the fundamental sympotms**, which are** particularly characteristic of sch, **and almost invariably present. These are the 4 A's.**

Associational Disturbances (Illogical or fragmented thought processes - **unrelated thoughts bound together**) – also primary – **it is reflected in incoherence**.
Affect **represents** the (Flattened or inappropriate emotional responses)
Autism **means a (preoccupation with internal stimuli** - withdrawal into private fantasy not consistent with logic)
Ambivalence **represents** (simultaneous, contradictory thinking, conflicting feelings toward others)

All the other symptoms like hallucinations, delusions, **or** catatonia **are**
Accessory symptoms which are shared with other disorders:

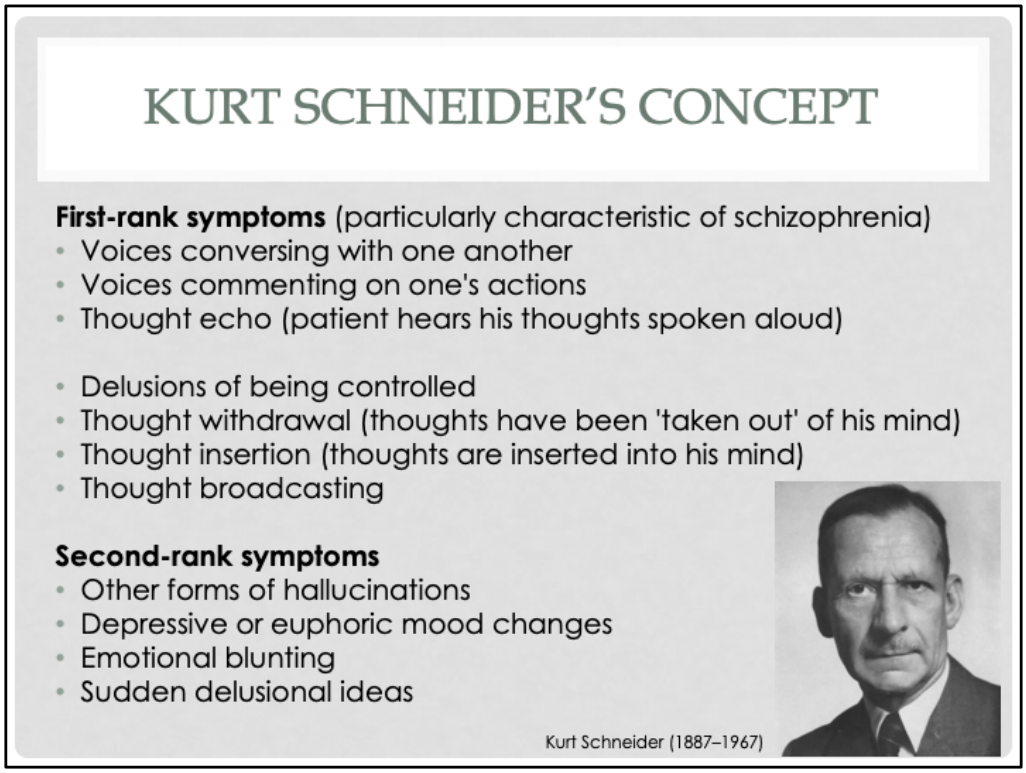
delusions, hallucinations, catatonia, **negativism, and stupor**

Despite the clinical diversity posited by Bleuler, he asserted that there were 4 cardinal features almost invariably present in schizophrenic patients. These have been termed the "four As":
Bleuler differentiated the symptoms or signs present in schizophrenia in 2 ways, as:

(1) fundamental (i.e., particularly characteristic of schizophrenia)
(2) accessory (shared with other disorders)

1. primary (directly due to an assumed organic deficit)
2. secondary (developing as a result of the primary disturbance—these included delusions and hallucinations).

4 A's were considered fundamental symptoms, only loosening of associations was also considered primary, making it the core deficit underlying schizophrenia.



Kurt Schneider also tried to identify the core symptoms of sch, that are particularly characteristic of sch. **He called them** First-rank symptom.

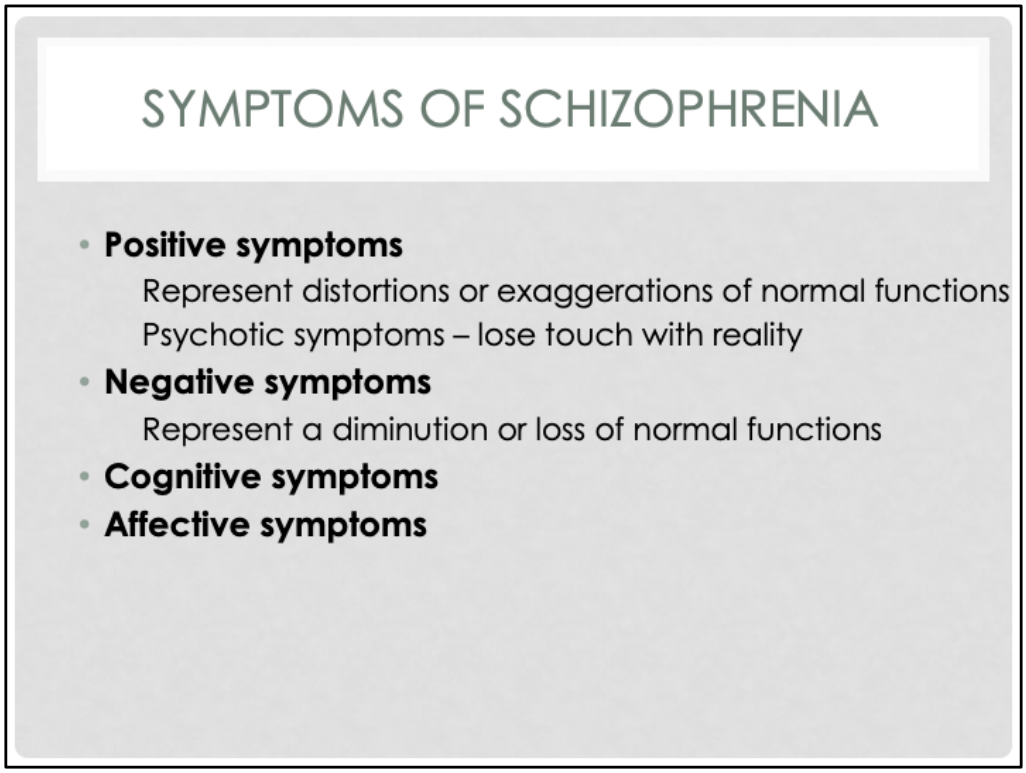
It involves special Auditory hallucinations:

- **When patients Hear** voices conversing with one another
- **Or when the patiens hear** Voices commenting on one's actions
- Thought echo **is an other example of FRSs when** the patient hears his **own** thoughts spoken aloud

Delusions being controlled **are frequent experiences in patients with sch**
Thought withdrawal **is a delusional belief that** thoughts have been 'taken out' of **patient's** mind
Thought insertion **is a delusional belief** that thoughts are inserted into the **patient's** mind)
Thought broadcasting **means that the patient thinks that his thoughts can be heard by others.**
Delusional perception (linking a normal sensory perception to a bizarre conclusion

All the other symptoms, like
other forms of hallucinations
depressive or euphoric mood changes
emotional blunting
sudden delusional ideas **are** Second-rank symptoms

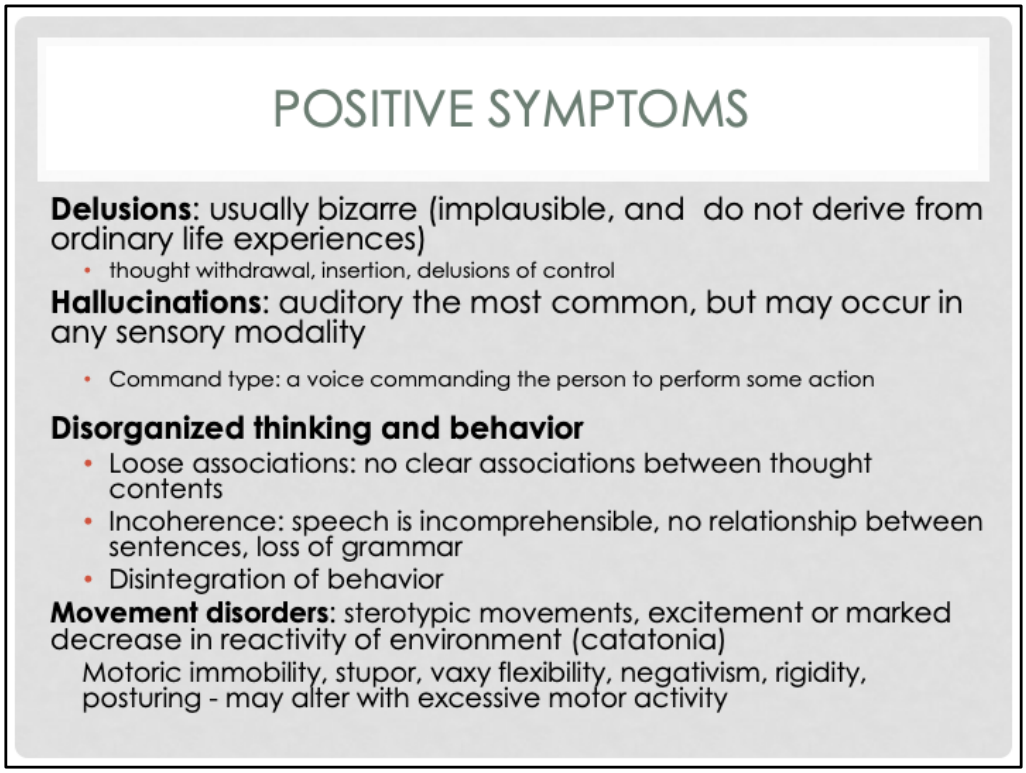
Perplexity - zavarodottság



There are 4 major symptom domain in sch.

Positive symptoms
Represent distortions or exaggerations of normal functions
They are Psychotic symptoms **when reality testing is impaired**
Negative symptoms
Represent a diminution or loss of normal functions
Cognitive symptoms **referes to the disturbances of thought processes, and the forth domain is**
Affective symptoms

Cognition: refers to the conscious mental operations involving the higher level, profoundly human abilities



People with schizophrenia can have delusions **that seem** bizarre**. They are** implausible **such as believing that neighbors can control their behavior with magnetic waves.**
Such delusions are the mentioned schneiderian first-rank symptoms. thought withdrawal, insertion, delusions of control

Delusions: false beliefs that are not accepted in the person's culture and do not change, that usually involve a misinterpretation of perceptions or experiences

Hallucinations:
The voices may talk to the person about his or her behavior, order the person to do things, or warn the person of danger. Sometimes the voices talk to each other. People with schizophrenia may hear voices for a long time before family and friends notice the problem.

Auditory hallucinations are by far the most common May occur in any sensory modality (e.g., auditory, visual, olfactory, gustatory, and tactile)

Command type **hallucination is when** a voice commanding the person to perform some action

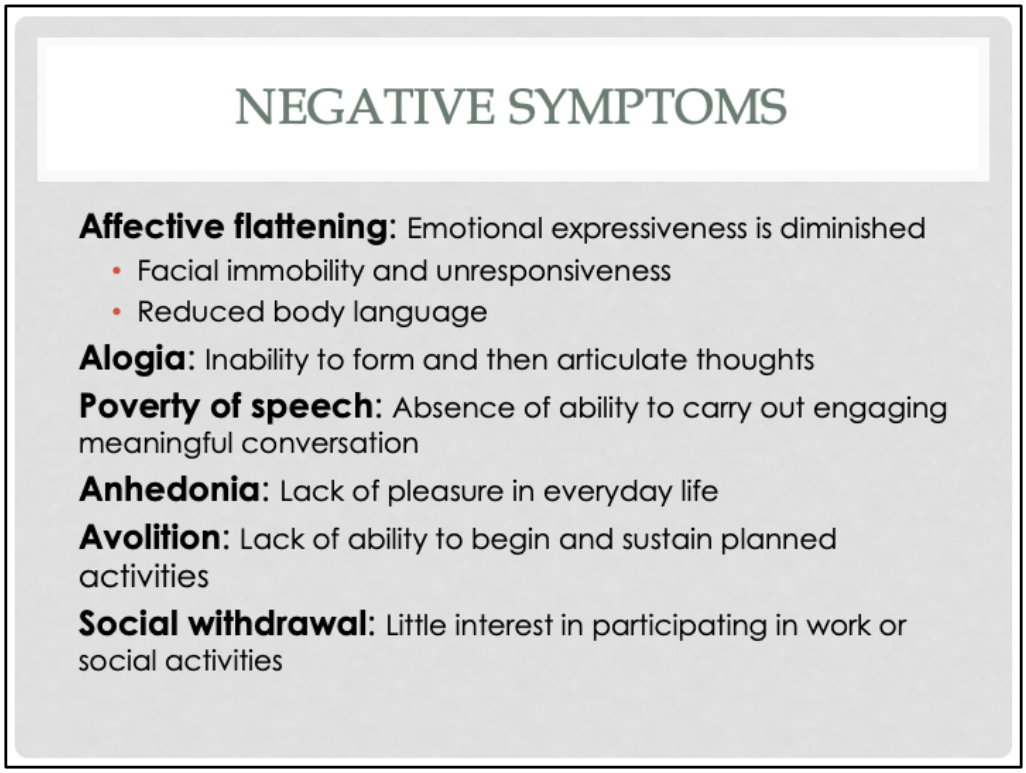
Next is Disorganized thinking and behaviour.
This is when a person has trouble organizing his or her thoughts or connecting them logically.
Loose associations: **is when there are** no clear associations between thought contents
Incoherence: **when the** speech is incomprehensible, **there is** no relationship between sentences, loss of grammar

Disorganized behavior **refers to the** Disintegration of behavior. **It can from childlike silliness to unpredictable agitation**
It may cause difficulties in performing activities of daily living

Movement disorder can range from excitement to marked decrease in reactivity. **Catatonia is characterized by marked decrease in reactivity to the environment.** stupor, vaxy flexibity, negativism, rigidity, posturing **are usual symptoms in catatonia. Catatonia** may alter with excessive motor activity.

A person with a movement disorder may repeat certain motions over and over. In the other extreme, a person may become catatonic.
Catatonia is characterized by marked decrease in reactivity to the environment. Someone with waxy flexibility, they would keep their arm where one moved it until it was moved again, as if it were made from wax.

Catatonic stupor: complete unawareness of the enviroment
Catatonic rigidity: maintaining a rigid posture and resisting efforts to be moved
Catatonic posturing: inappropriate or bizarre postures
Catatonic excitement: purposeless and unstimulated excessive motor activity



Negative symptoms are associated with disruptions to normal emotions and behaviors. These symptoms are harder to recognize as part of the disorder and can be mistaken for depression or other conditions.

Affective flattening **means that** Emotional expressiveness is clearly diminished.
Patients usually exhibit facial immobility and unresponsiveness, and **they talk in a dull or monotonous voice.**

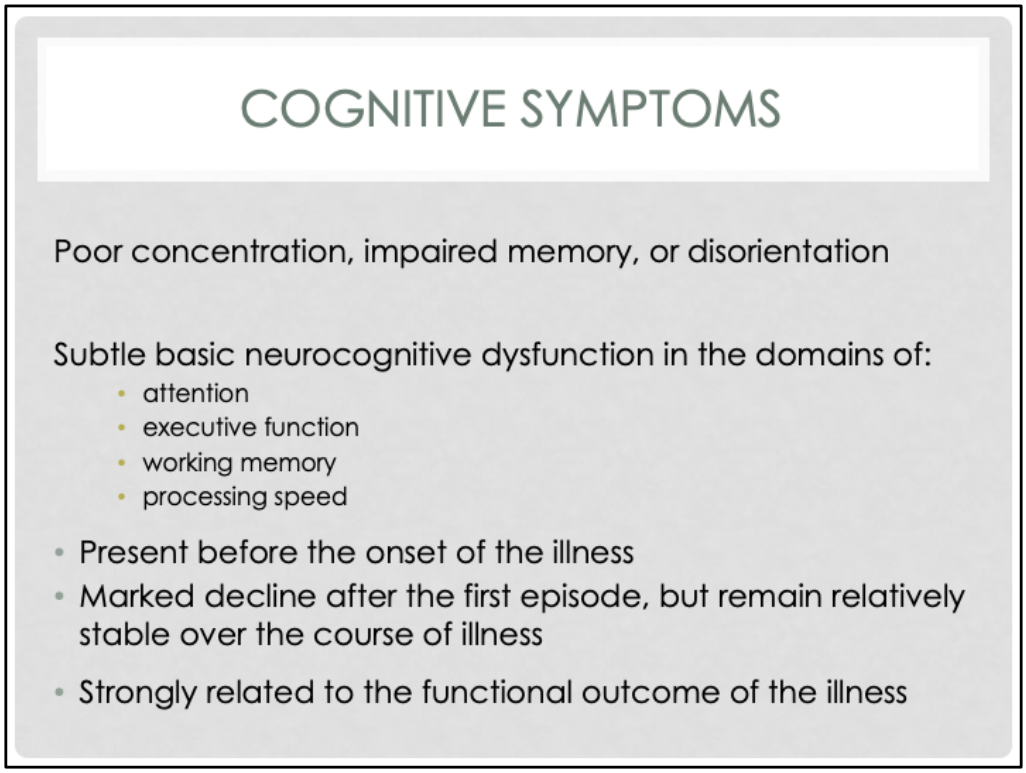
Flat affects also refelected in reduced body language.

Alogia: **refers to the** inability to form and then articulate thoughts.
Poverty of speech: **means the** absence of ability to carry out engaging meaningful conversation.

People with sch may experience anhedonia: **which is the** Lack of pleasure in everyday life.

Avolition **is alo a frequent negative symptom, which refers to the** lack of ability to begin and sustain planned activities.

Social withdrawal **is frequent symptom**. **Patients have** little interest in participating in work or social activities.



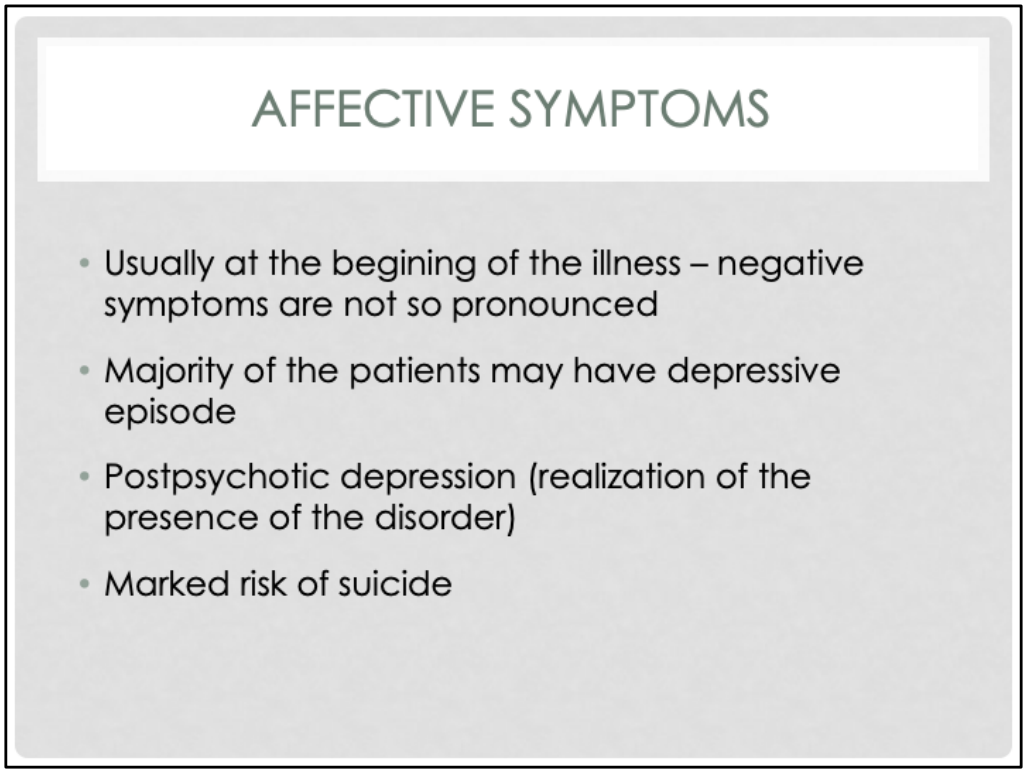
We can detect as poor concentration, disorientation, or impaired memory on the level of symptomatology.

Cognitive deficits are based on subtle basic neurocognitive dysfunction. **Neurocognitive symptoms may be difficult to recognize as part of the disorder. Often, they are detected only when other tests are performed.**
The most important deficits are:

attention
executive function (the ability to understand information and use it to make decisions)
working memory (the ability to use information immediately after learning it)
processing speed
verbal and visual learning

Neurocognitive deficits are Present before the onset of the illness, **and usually there is a** Marked decline after the first episode.
Usually it Remain stable over the course of early illness in most of the patients, **however a small portion of the patient exhibit progressive decline in cogntivie functioning.**

Cogntivie symptoms are very important, because they are Strongly related to the functional outcome of the illness. They have even greater impact on everyday functioning than positive symptoms.



Affective symptoms are usually more frequent at the begining of the illness, **when** negative symptoms are not so pronounced (like flat affects).

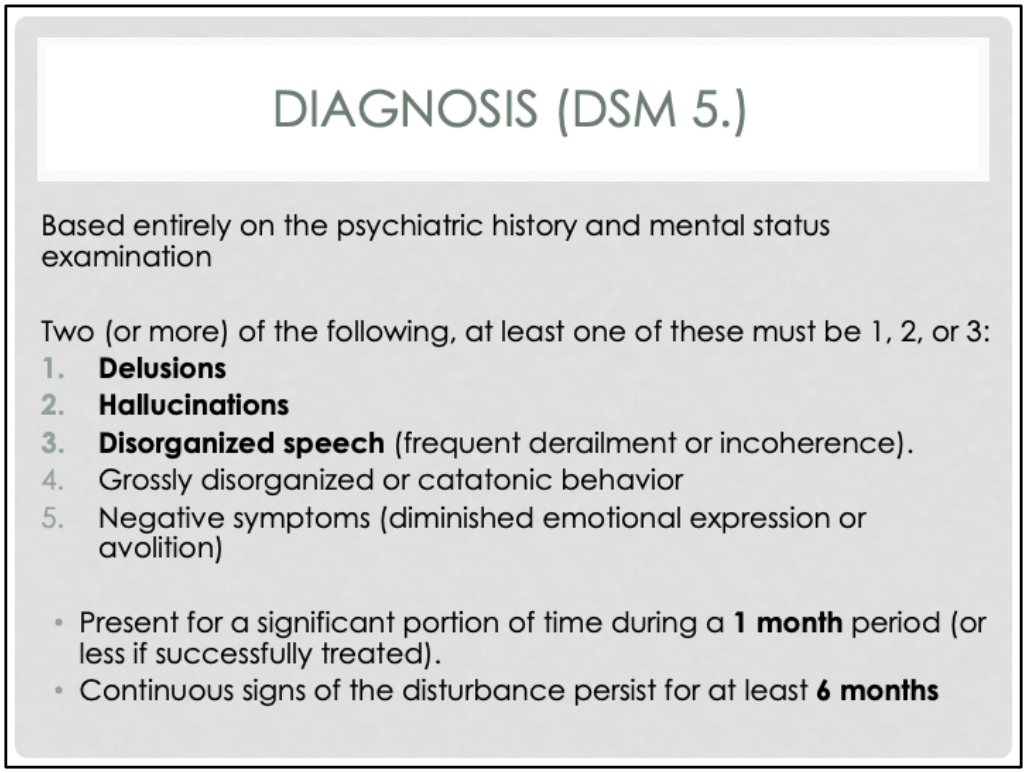
However epidemiological studies indicate that majority **(up to 80 percent) of schizophrenia** patients may have a major depressive episode **at some time in their lives.**

Depression is more likely to occur after the psychotic episode as a

Postpsychotic depression (**and it is usually reflects the** realization of the presence of the disorder). **Postpsychotic period means a higher vulnerablity to depression**. **Dysphoric mood may take the form of depression, anxiety, or anger. Sleep patterns are often disturbed.**

It associate with marked risk of suicide.

Suicide is the single leading cause of premature death among people with schizophrenia. It is about 4-10%.



Diagnosis of schizophrenia is based entirely on the psychiatric *history* and *mental status* examination.

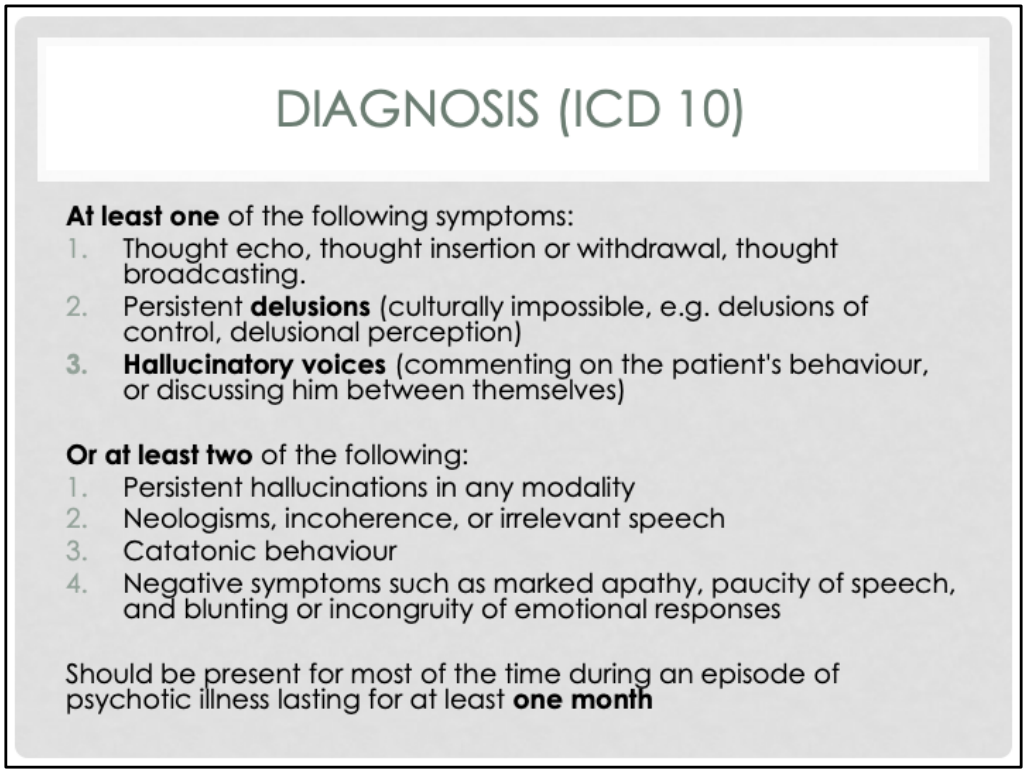
There is *no laboratory test* for schizophrenia.

Two (or more) of the following **symptoms must be present**, at least one of these must be **from the first 3 symptoms**:

1. **Delusions**
2. **Hallucinations**
3. **Disorganized speech** (frequent derailment or incoherence).
4. Grossly disorganized or catatonic behavior
5. Negative symptoms (diminished emotional expression or avolition)

The symptoms must be Present for a significant portion of time during a 1 month period (or less if successfully treated).
Continuous signs of the disturbance persist for at least 6 months, **and may include periods of prodromal or residual symptoms.**

This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet active-phase symptoms, and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by **only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).**

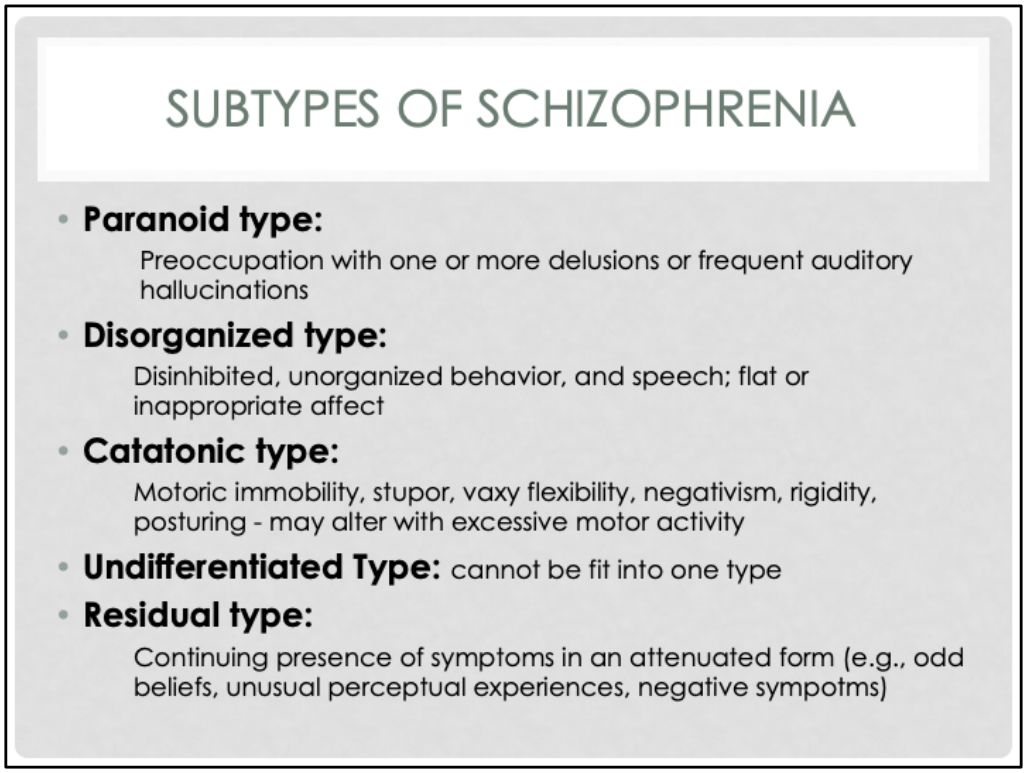


The ICD diagnosis allows the presence of only one symptom, if it is clearly a characteristic shneiderian schizophrenic symptoms like:

1. Thought echo, thought insertion or withdrawal, thought broadcasting.
2. Persistent delusions (culturally impossible, e.g. delusions of control, delusional perception – delurional misinterpretation of normal peceptions)
3. Hallucinatory voices (commenting on the patient's behavior, or discussing him between themselves)

Or at least 2 symptoms
Persistent hallucinations in any modality
Formal thought disorder, like Neologisms, incoherence, or irrelevant speech
Catatonic behavior
Or negative symptoms

According to ICD 10 Symptoms must be present at least one month according to ICD 10 criteria.



Subtymes are eliminated in DSM 5 due to their limited diagnostic stability, low reliability, and poor validity. They also have not been shown prognostic value in terms of treatment response.

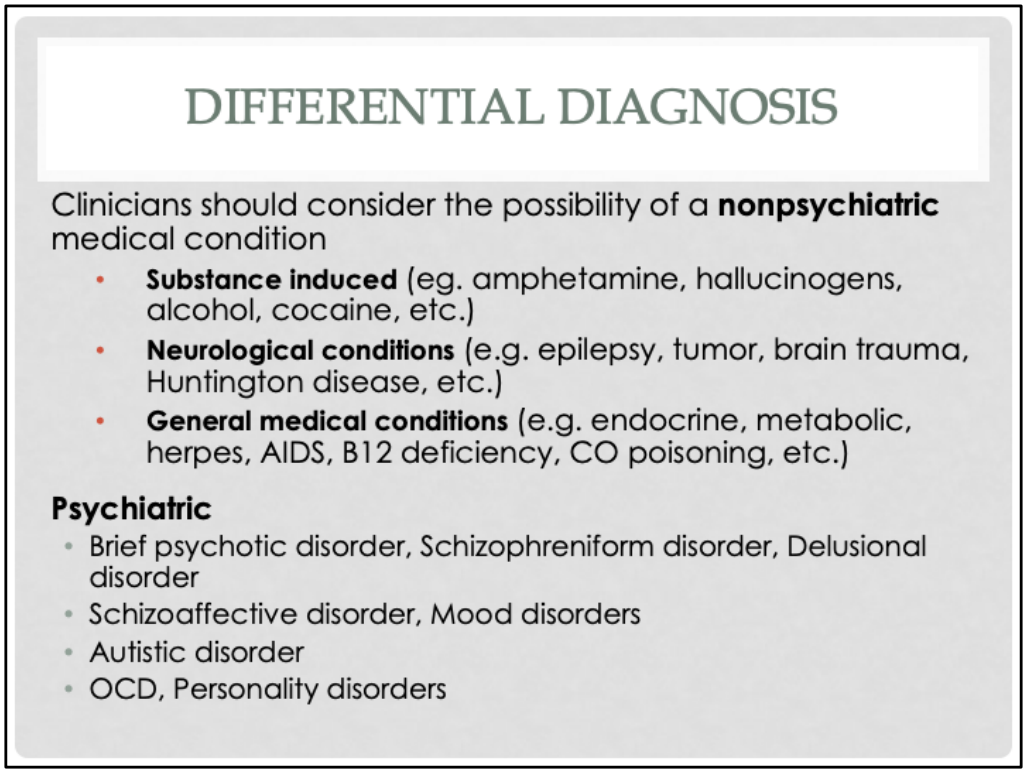
Paranoid type is characterized by delusions and frequent auditory hallucinations.

Disorganized type **is characterized by**
Marked regression to primitive, disinhibited, and unorganized behavior
Usually active but in an aimless, nonconstructive manner

Catatonic:
The catatonic type of schizophrenia, which was common several decades ago, has become rare in Europe and North America. The classic feature of the catatonic type is a marked disturbance in motor function; this disturbance may involve stupor, negativism, rigidity, excitement, or posturing (Fig. 13-6). **Sometimes, the patient shows rapid alteration between extremes of excitement and stupor.** Associated features include stereotypies, mannerisms, and waxy flexibility. Mutism is particularly common. During catatonic excitement, patients need careful supervision to prevent them from hurting themselves or others. Medical care may be needed because of **malnutrition, exhaustion, hyperpyrexia, or self-inflicted injury.**

Undifferentiated Type: **when the predominant sympotms** cannot be fit into one type.

Residual:
characterized by continuing presence of symptoms **in the absence of a complete set of active symptoms or of sufficient symptoms to meet the diagnosis of another type of schizophrenia**. Emotional blunting, social withdrawal, eccentric behavior, illogical thinking, and mild loosening of associations commonly appear in the residual type. When delusions or hallucinations occur, they are neither prominent nor accompanied by strong affect. **Substantial proportion of patients exhibit residual symptoms, especially negative symptoms.**



clinicians should **always** consider the possibility of a nonpsychiatric medical condition, even in patients with previous diagnoses of schizophrenia

1. Substance induced psychotic **states can resemble to sch** —amphetamine, hallucinogens, belladonna alkaloids, alcohol hallucinosis, barbiturate withdrawal, cocaine, phencyclidine – **somatic symptoms and toxicology may aid the proper dg.**

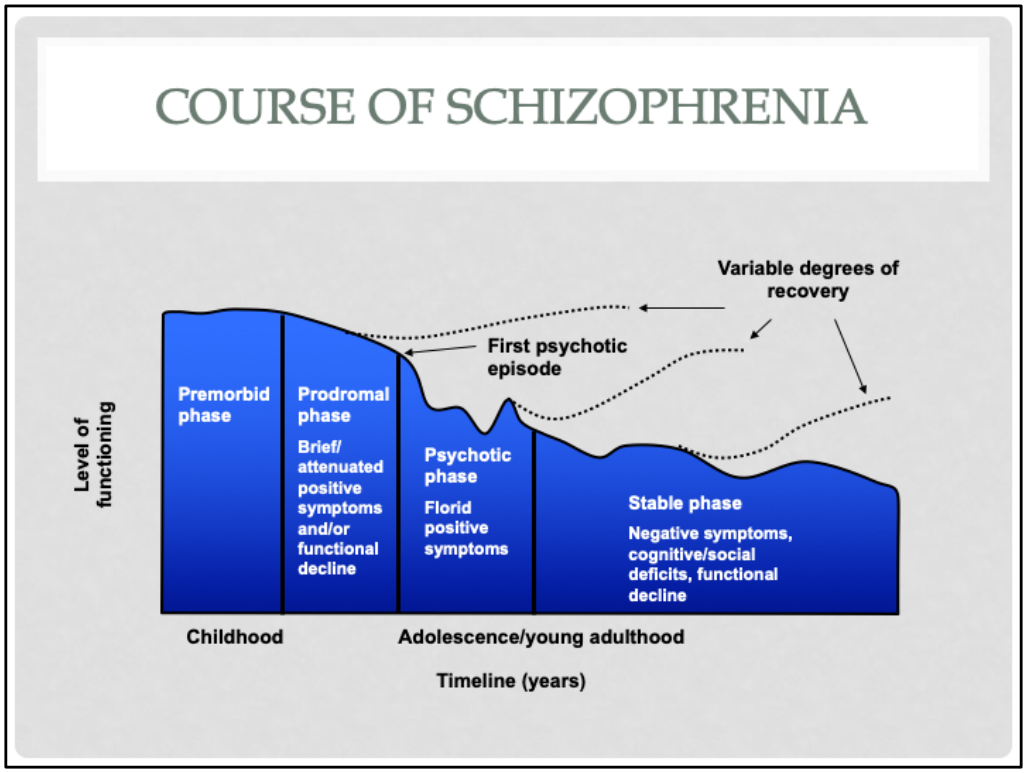
2. Neurological conditions **may also mimic sch**
Epilepsy—especially temporal lobe epilepsy, Neoplasm, cerebrovascular disease, or trauma—especially frontal or limbic **must be excluded**
Neurological signs, EEG, and imaging methods (CT or MRI) helps in differentiation.

3. General medical conditions **are also important**. **usually somatic symptoms, lab test can aid the proper dg.**

We should also exclude other types of psychiatric disorders.
Brief psychotic disorder, Schizophreniform disorder – **symptoms are present for a shorter period of tim**e, **Delusions** in Delusional disorder **are usually not bizarr**, Schizoaffective disorder **and**
Mood disorders **characterized by prominent affective symptoms**.
The onset of Autistic disorder **is in the early childhood**, **and rarely associate with hallucinations and delusions.**
OCD, Personality disorders **– can be differentiate by the lack of psychotic symptoms.**

Personality disorders —schizotypal, schizoid, borderline, paranoid

Acute intermittent porphyria
AIDS
B_{12} deficiency
Carbon monoxide poisoning
Cerebral lipoidosis
Creutzfeldt-Jakob disease
Fabry's disease
Fahr's disease
Hallervorden-Spatz disease
Heavy metal poisoning
Herpes encephalitis
Homocystinuria
Huntington's disease
Metachromatic leukodystrophy
Neurosyphilis
Normal pressure hydrocephalus
Pellagra
Systemic lupus erythematosus
Wernicke-Korsakoff syndrome
Wilson's disease



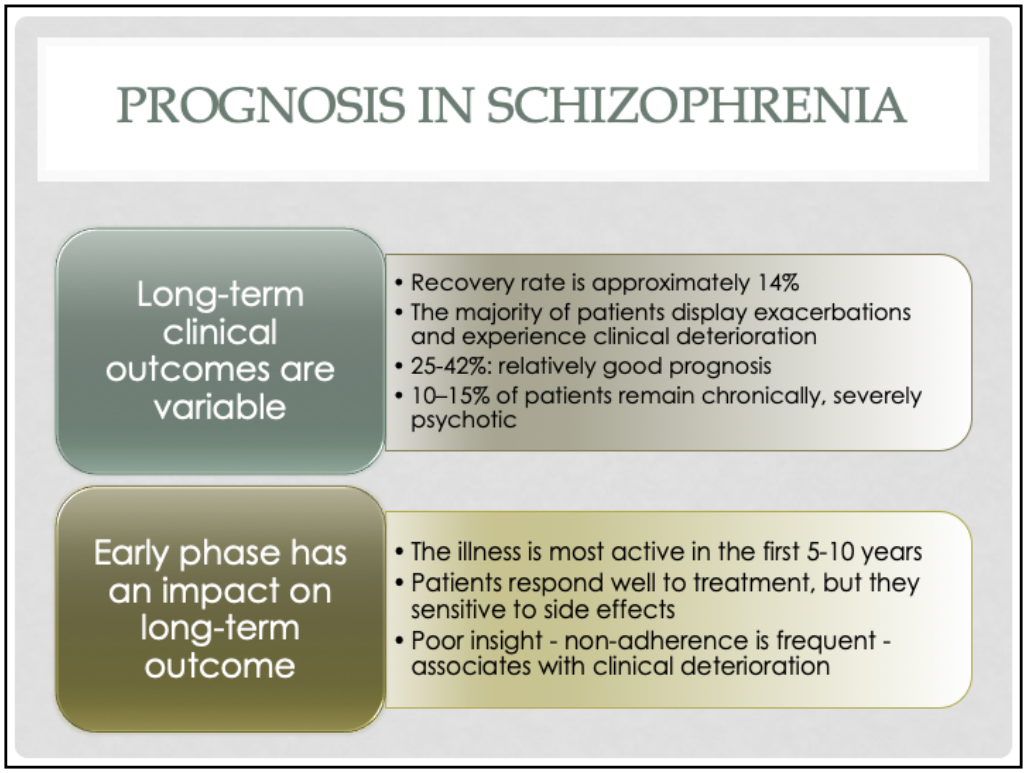
The course of Schizophrenia can be divided into 4 phases
1. A **premorbid phase** with subtle and non-specific cognitive, motor and/or social dysfunction

2. A **prodromal phase** characterized by **brief positive symptoms and/or a decline in a person's level of functioning**

3. The first **psychotic** episode that signals the onset of schizophrenia
   - **The initial years of the illness are characterized by repeated episodes of psychosis with inter-episode remission. The repeated relapses usually cause deterioration in functioning.**
   - The illness is most active in the first 5-10 years after a first episode of psychosis.

4. In the **stable phase** the psychotic symptoms are less prominent. This is also associated with increasingly predominant negative symptoms and functional decline.

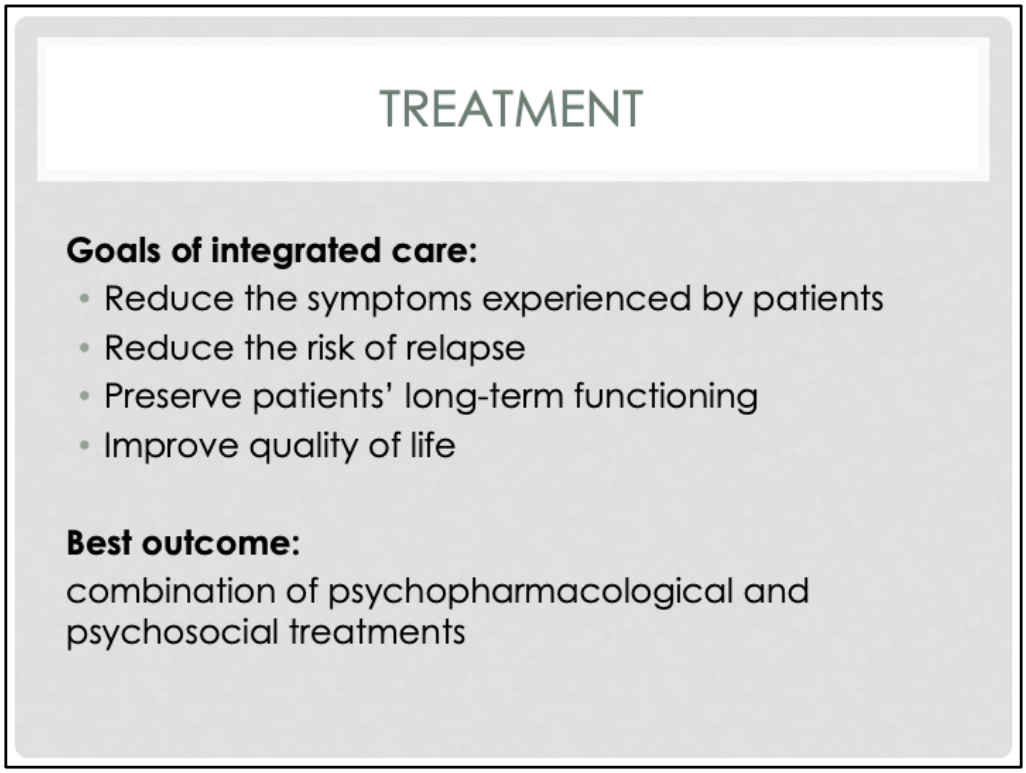
However, adequate treatment in the early phase may prevent the deterioration of the functionality, and may ensure remission.



Long-term clinical outcomes are variable:
Recovery rate is approximately 14%
The majority of patients display exacerbations and experience clinical deterioration
25-42% of the **patients have relatively** good prognosis, **and**
10–15% of patients remain chronically, severely psychotic

The early phase has a marked impact on long-term outcome. The illness is most active in the first 5 years

In this phase the patients respond well to treatment, but **they also** sensitive to side effects, **and they** have a poor insight. Non-adherence to treatment is quite frequent, and **treatment discontinuation results in relapses**. **Relapses** associate with clinical deterioration

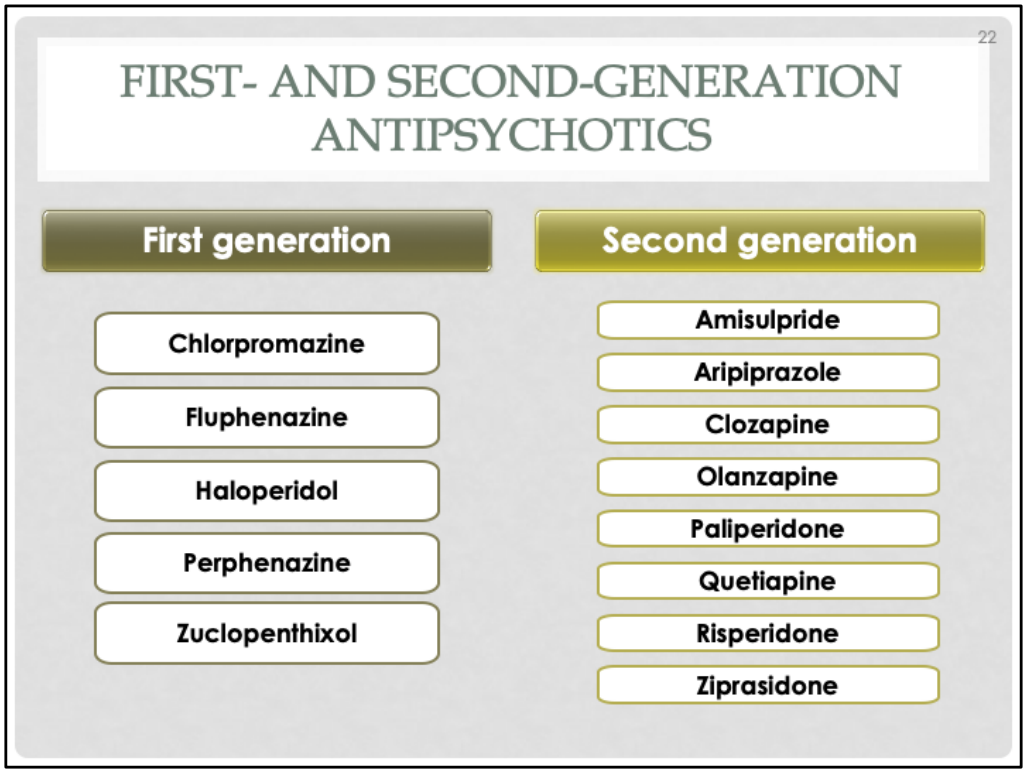


The treatment of sch requires integrated care

The goals of **this** integrated care are:

- **The treatment have to** reduce the symptoms experienced by patients.
- **It is also important to** Reduce the risk of relapse, **as each relapse delays the hope of remission.**
- **The enduring remission helps to** Preserve patients' long-term functioning.
- **And finally the goals also involve the** Improve**ment of** quality of life.

Best outcome **can be achieved by the**
combination of psychopharmacological and psychosocial treatments.



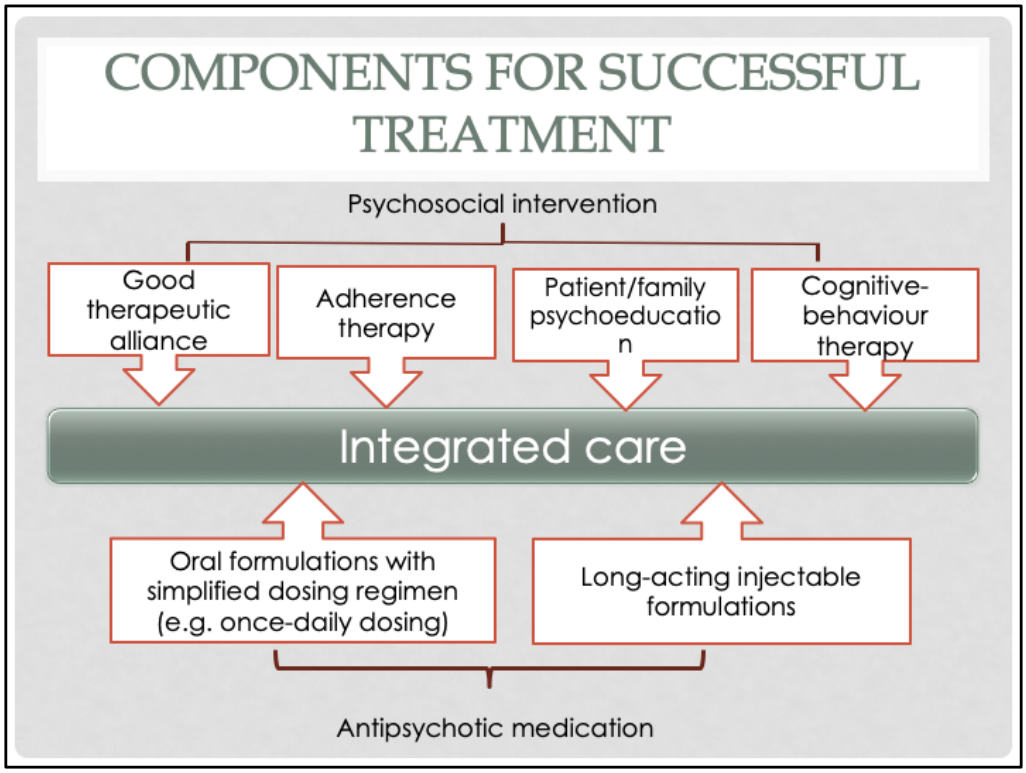
According to the DA hypothesis, the pharmacological treatment means the use of antipsychotics. The main therapeutic effect is linked D2 receptor blockade.

FGAs are blocking the same number of D_2 receptors in all brain areas. It means that they effectively reduce positive symptoms, but usually associate with EPS, and elevation of PRL level. This undifferentiated effect may be responsible for the worsening of cognitive and negative symptoms.

However, **SGAs** has a differential effect in different brain areas, which means that they block the D2 receptors in DA pathway responsible for positive symptoms in a greater extent (namely the in the mesolimbic pathway), then in the other DA pathways, and so they also improve the negative and cognitive symptoms, although these effect is not so pronounced on these symptoms, as it is on positive symptoms. They also rarely cause EPS or hyperprolactinemia.

Weight gain, insulin resistance, hyperglycemia, dyslipidemia, and type 2 diabetes mellitus, cardiovascular side effects (hypertension and arrhythmias)

The overall goal of pharmacological treatment is:
- to **reduce the activity of hyperactive pathways** mediating psychosis
- and **to increase the activity of hypoactive pathways** that seem to mediate negative and cognitive symptoms,
- while simultaneously **preserving the activity of those pathways that regulate motor movement and prolactin secretion**.



The antipsychotic medication is the cornerstone of the treatment. However due to their poor insight and impaired cognitive functions patients tend to stop medication. We should suggest **simplified dosing regimen** to promote medication adherence,

We should choose **long acting injections** if the patients is non-compliente. It means, that the drug is surely present, so we can adequately assess the efficacy, and we can detect non-compliance immediately, so we can initiate preventive steps to avoid relapse.

Pharmacotherapy alone is not enough. We have to supplement the pharmacotherapy with some kind of psychosocial intervention.

1. The good therapeutic alliance is the basis of the treatment. It means a trustful partnership, when we should emphasize the shared decision making.
2. However, the poor insight usually makes it necessary to motivate the patient participation in the therapeutic process to enhance the adherence to the medication.
3. Psychoeducation is important in supplying the patient and his family with information about the illness (e.g. symptoms, early signs of the acute relapses, etc.). It is also important to educate patient about benefits of medication and possible side effects.
4. Cognitive-behaviour therapy is useful in finding coping strategy with the positive or negative symptoms.