Psychopharmacology and Pharmacotherapy of Schizophrenia

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1. Introduction

The image shown above represents an artificial intelligence (AI) interpretation of schizophrenia. It provides a good impression of the divisiveness and chaos this illness can bring.
This book provides insight into the psychopharmacology and pharmacotherapy of antipsychotics, the main therapy for schizophrenia, a disease controversial because of its disease-laden name. Nowadays, it is also called psychosis sensitivity syndrome. A different name doesn't change the suffering that accompanies it.

The outlined and described developments in psychopharmacology and pharmacotherapy over the past seven decades have had an enormous impact on the lives of patients and their families.

While in earlier centuries this illness was surrounded by an aura of decay and putrefaction, its image has changed dramatically over the past 60 years thanks to the use of specialized medications known as antipsychotics. Increasing knowledge about the psychopharmacology of antipsychotics has been accompanied by an increase in knowledge about the nature and background of schizophrenia.

This book first describes schizophrenia from a pharmaceutical perspective, including its symptomatology, the known schizophrenia hypotheses, and the etiology of this mental illness. The psychopharmacology and pharmacotherapy of antipsychotics are then described (early developments, conventional antipsychotics, atypical antipsychotics, and future developments). The development of adjuvant treatment options is also described. Non-pharmacological treatment options are also briefly mentioned. Below are some concluding remarks. This book provides insight into the chemistry, psychopharmacology, and pharmacotherapy of antipsychotics, as well as the symptoms, background, causes, and treatment of schizophrenia.

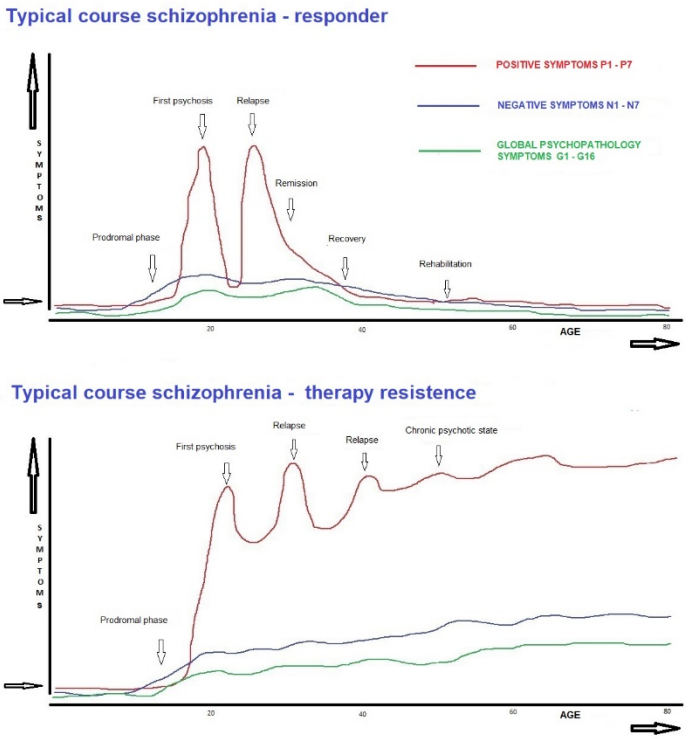
2. The disease schizophrenia. Symptoms

Symptoms of schizophrenia can be very severe. Below is a list of possible symptoms that can occur to varying degrees in schizophrenia, a complex illness, that much is clear. It is also possible that certain symptoms are absent. Some (groups of) symptoms can be striking in a patient. Schizophrenia symptoms can be scored according to the PANSS. PANSS stands for Positive and Negative Syndrome Scale. Due to the variable presentation, variations in possible increases in PANSS (from mild to severe), schizophrenia is often not considered a single disease, but a group of related diseases (a syndrome). Antipsychotics can significantly reduce PANSS scores to normal (PANSS scores 1 to 2 (absent to minimal) per item), which is reflected in clinical remission to clinical recovery. Certain antipsychotics can, in particular, normalize certain symptoms, so it is important to find optimal treatment that addresses the specific symptomatology. Accurate diagnosis and careful selection of the antipsychotic are therefore essential. This is the work of qualified psychiatrists.

Positive scale	Global Psychopathology scale
1.Delusions	1.Somatic concern
2.Conceptual disorganization	2.Anxiety
3.Hallucinations	3.Guilt feelings
4.Excitement	4.Tension
5.Grandiosity	5.Mannerisms and posturing
6.Suspiciousness/persecution	6.Depression
7.Hostility	7.Motor retardation
	8.Uncooperativeness
Negative scale	9.Unusual thought content
1.Blunted affect	10.Disorientation
2.Emotional withdrawal	11.Poor attention
3.Poor rapport	12.Lack of judgment and insight
4.Passive/apathetic social withdrawal	13.Disturbance of volition
5.Difficulty in abstract thinking	14.Poor impulse control
6.Lack of spontaneity and flow of conversation	15.Preoccupation
7.Stereotyped thinking	16.Active social avoidance

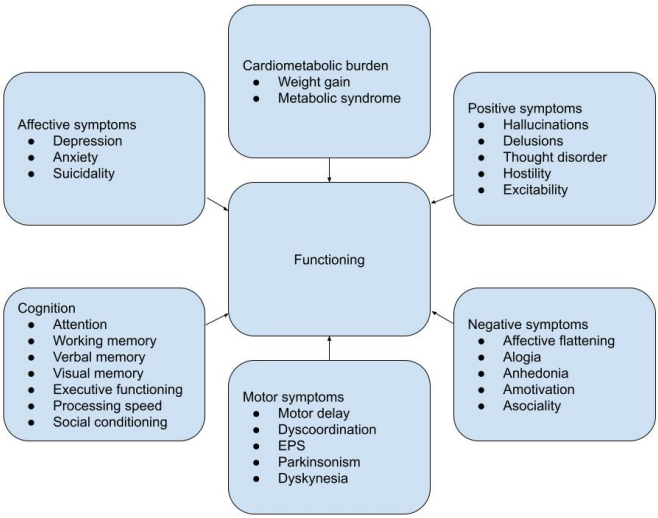
These are the items recorded in the PANSS symptom score. Symptoms can be divided into positive, negative, and global psychopathological symptoms. The items are scored on a scale ranging from 1 (absent) to 2 (minimal), 3 (mild), 4 (moderate), 5 (moderately severe), 6 (severe), and 7 (extreme). All values (P1-P7, N1-N7, and G1-G16) together form the Total PANSS score (minimum 30, maximum 210). The SAPS (Scale for the Assessment of Positive Symptoms) is a subscale for positive symptoms, and the SANS (Scale for the Assessment of Negative Symptoms) for negative symptoms. The PANSS Global measures global psychopathological symptoms. The possible scores of 1-7 indicate that there are completely different presentations, degrees of severity, and variations in the illness. Furthermore, not all of the items listed above necessarily score higher. The more relapses, the harder it is to lower PANSS scores. This will take longer or may not even happen.

Graphical representation of a typical course of schizophrenia in a responder and in treatment-resistant schizophrenia (approximately 20% of cases):



Affective and cognitive symptoms are included in the global psychopathological symptoms. Antipsychotics will certainly reduce the scores and, above all, improve the patient's condition. Conventional antipsychotics effectively combat positive symptoms. Atypical antipsychotics also do this and are also somewhat

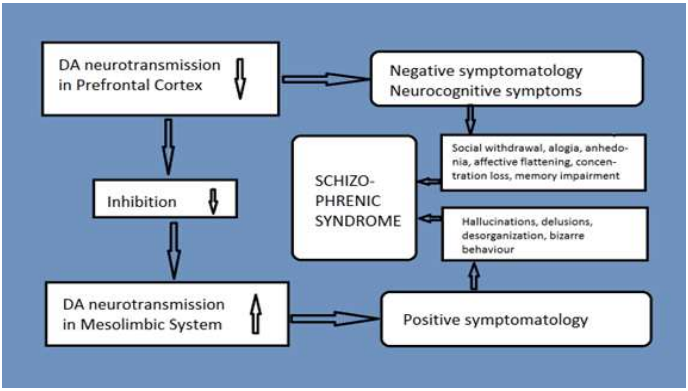
effective against negative, affective, and cognitive symptoms.
Adjuvant therapies can have an additional effect on symptom reduction. Over time, symptom scores can decrease further. Non-pharmacological treatment options can also contribute to this. Lowering symptom scores with antipsychotics contributes significantly to the quality of life of patients and their families. Effective antipsychotic medication and therapies are crucial.
Schizophrenia is a common illness and is usually relatively well-treated with medication. In addition to remission and recovery, social and vocational rehabilitation are initial treatment goals.
Both the clinical symptoms of schizophrenia and comorbid factors have a significant impact on social and work functioning. This can compromise the ability to care for oneself. Effective treatment of the symptoms of the disease can significantly improve these areas. The absence of certain symptoms and comorbid factors also benefits the course and prognosis of the disease.
Negative and cognitive symptoms are the most important markers of patients' quality of life and largely determine the degree of disability. The worse the initial baseline condition at the start of treatment, the longer and more difficult the road to remission, recovery, and rehabilitation will be. The sooner treatment is initiated, the better for a good outcome. Effective treatment of negative and cognitive symptoms is still in its early stages in practice, but developments are expected in the coming years.


Cardiometabolic burden
Weight gain
Metabolic syndrome
Affective symptoms
Depression
Anxiety
Suicidality
Positive symptoms
Hallucinations
Delusions
Thought disorder
Hostility
Excitability
Functioning
Cognition
Attention
Working memory
Verbal memory
Visual memory
Executive functioning
Processing speed
Social conditioning
Negative symptoms
Affective flattening
Alogia
Anhedonia
Amotivation
Asociality
Motor symptoms
Motor delay
Dyscoordination
EPS
Parkinsonism
Dyskynesia

3. Schizophrenia hypotheses

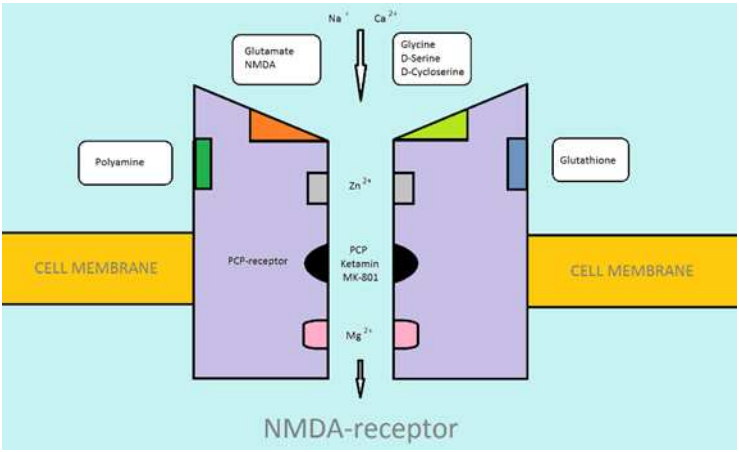
The main hypotheses for the background and causes of schizophrenia are the dopamine hypothesis of schizophrenia, the more recent glutamate hypothesis of schizophrenia, and the kynurenic acid hypothesis of schizophrenia. Conventional and most atypical antipsychotics were developed based on the dopamine hypothesis of schizophrenia. Currently, agents based on the glutamate hypothesis of schizophrenia have also been developed, which provides a more complete explanation of the illness. The glutamate hypothesis is also called the NMDA receptor hypothesis of schizophrenia. The kynurenic acid hypothesis is a further development of the glutamate hypothesis.

Dopamine:



Schizophrenia can—in theory—be considered a complex of compound effects: on the one hand, reduced dopaminergic neurotransmission in the prefrontal cortex (PFC) and, on the other, increased dopaminergic neurotransmission in the limbic system. This is an indirect consequence of the reduced neurotransmission in the PFC, as the PFC's inhibition of the limbic system in the brain is reduced under the influence of the reduced dopamine neurotransmission in the PFC. The consequences are positive, negative, and neurocognitive symptoms, all of which can occur in schizophrenia. This is called the dopamine hypothesis of schizophrenia. The Positive and Negative Syndrome Scale (PANSS) is a tool for determining the extent to which these symptoms occur, in order to identify and quantify the effects of treatments. The resulting imbalance is thought to be caused by underlying influences on glutamatergic neurons.
The 5-HT2A antagonistic properties of many atypical antipsychotics promote an increase in DA activity in the PFC, which has a beneficial effect on the disease.
It is now thought that psychotic symptoms originate in the associative striatum.

Glutamate:



Above is a simplified schematic representation of the NMDA receptor, including an ion channel in the nerve cell membrane.
There are several so-called binding sites for different substances within the NMDA receptor, as indicated, all of which can influence its function. According to the glutamate hypothesis of schizophrenia, hypofunction of the NMDA receptor leads to the symptoms of schizophrenia. This hypofunction can be modulated in various ways via the binding sites. Simultaneous binding of glutamate and one of the other ligands is required for an effect. It has also long been known that a severe magnesium deficiency (hypomagnesemia) can lead to psychosis. This may be related to the binding site on the NMDA receptor. Magnesium also acts as a natural positive allosteric modulator on the NR2B subtype of the

NMDA receptor. PCP is phencyclidine (Angel Dust), a so-called street drug that can evoke a complete picture of schizophrenia (including positive, negative, and neurocognitive symptoms). Ketamine has a similar effect.

These substances are also used in preclinical models of schizophrenia in the laboratory. Special binding sites for these schizophrenogenic substances are present in the ion channel of the NMDA receptor. Recent research has shown that antibodies against the NMDA receptor are present in approximately 10% of schizophrenia cases. The precise immune complications of this are not yet fully understood, but the antibodies can also cause NMDA receptor hypofunction. As such, schizophrenia can be considered more or less an autoimmune disease, and in some cases, immunotherapy may be an option. Since 2007, another disease has been known, anti-NMDA receptor encephalitis, in which antibodies to the NMDA receptor produce a schizophrenia-like picture. In that case, treatment is different.