

Schizophrenia: Etiology, Pathophysiology and Management - A Review

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ABSTRACT

Introduction: Diagnosis of schizophrenia is largely a clinical assessment of a group of signs and symptoms. There are various factors that can be a cause or a risk factor for creating this disorder; some preventable and some non-preventable. The treatment options are diverse and are continuously being studied in order to enhance results and minimize adverse effect of various forms of therapy.

Methodology: We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1987, through March 2017. The following search terms were used: schizophrenia, etiology of schizophrenia, pathophysiology, clinical features, and treatment of schizophrenia

Aim: Our aim in this study was to understand the etiology, pathophysiology, and study various lines and advancement in management of schizophrenia. **Conclusion:** In the recent years, many treatment options are emerging where newer drugs and their combination with or without non-pharmacological therapy have shown promising results. More studies must be done to implement advanced regimens for treatment of schizophrenia.

Keywords: schizophrenia, genetic cause of schizophrenia, pharmacologic management of schizophrenia

INTRODUCTION

The fundamental features of Schizophrenia are:

1. **Positive symptoms** which include delusions and hallucinations, also called the psychotic symptoms where there is a loss of contact with reality.
2. **Negative symptoms** which includes in specific impaired motivation, drop in spontaneous speech, social withdrawal.
3. **Cognitive weakening.**

The positive symptoms have a tendency to relapse and remit, although some patients feel residual prolonged psychotic symptoms. The negative and cognitive symptoms have a tendency to be chronic and are related to long-term effects on societal function. Cognitive signs are the up-to-date classification in schizophrenia. These symptoms are not specific and therefore, they should be severe enough for the others to notice them. Cognitive symptoms comprise disorganized speech, attention, and thought, eventually impairing the person's capability to communicate^[1].

Among additional abnormal (schizoid) actions, social withdrawal usually leads a person's first psychotic episode; nevertheless, some patients

may show no symptoms at all. A psychotic episode is described by patient-specific symptoms

and signs (known as psychotic features) that mirror the "false reality" formed in the patient's awareness. The first episode of psychosis typically happens in late adolescence or early adulthood but is often headed by a prodromal phase known as "at risk mental state".

Additionally in some examples premorbid impairments in social functioning and/ or cognition go back several years. Still, in other examples onset is abrupt in formerly well-functioning individuals^[2].

Substance-abuse disorders happen most frequently amongst these patients; such disorders can involve a range of substances, which includes alcohol, prescription medication, and tobacco. Anxiety, obsessive-compulsive disorder, depression, and panic are also noticeable in patients with schizophrenia and may worsen the symptoms of their disorder. Such patients also have an overall lack of mindfulness of their disease. This mindset has been associated to great rates of non-adherence, poor psychosocial

function, relapse, bad hygiene, and worse disease prognosis^[3].

The prognosis for patients with schizophrenia is usually unpredictable. Merely 20% of patients notice favorable treatment results. The other patients experience many psychotic episodes, long term symptoms, and a meager response to antipsychotics^[1]. In this review we will study the etiology, pathophysiology, and management of schizophrenia.

METHODOLOGY

•Data Sources and Search terms

We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1987, through March 2017. The following search terms were used: schizophrenia, etiology of schizophrenia, pathophysiology, clinical features, and treatment of schizophrenia.

•Data Extraction

Two reviewers have independently reviewed the studies, abstracted data, and disagreements were resolved by consensus. Studies were evaluated for quality and a review protocol was followed throughout.

The study was done after approval of ethical board of King Abdulaziz University.

ETIOLOGY

Genetics

Though genetic studies have evidently recognized a genetic origin for the schizophrenia spectrum of disorders, the character of these genetic reasons and their variety of phenotypic expression continue to be unclear. The study of schizophrenia in identical twins also proposes that other non-genetic factors must impact the expression of this illness^[3]. Both family and adoptive studies propose a bigger prevalence of schizotypal personality disorder among the relatives of the patients with schizophrenia compared to control groups. In case of monozygotic twins, the possibility of one twin suffering from schizophrenia is as high as 48% if the other twin has the disorder, while the risk is 12% - 14% among dizygotic twins. In case of both parents having schizophrenia, the possibility that their child will suffer from schizophrenia is around 40%^[4].

There is evolving proof that the deficit-like and psychotic-like symptoms might have autonomous heritability in both normal and schizophrenia spectrum subjects. The twin studies of normal subjects and family studies of schizophrenic patients with propose that there are at least two heritable influences in schizophrenia: - related to the positive symptoms and - related to the cognitive impairment and negative symptoms of the spectrum^[5].

The frequency of both the schizophrenia-related personality disorders and psychosis are higher among the relatives of schizophrenia probands as compared to among the relatives of affective disorder probands, however the schizophrenia spectrum personality disorders, categorized by eccentricity and social deficits, and psychotic disorders do not essentially happen between the same relatives. These data are in agreement with partially independent transmission of one set of genetic factors mutual to the spectrum that mostly manifest in social and cognitive deficits and among another set of separate genetic factors associated to psychosis^[5].

Developmental and Environmental Factors

The leading example for analyzing the environmental factors that contribute to schizophrenia etiology for three decades has been the neurodevelopmental hypothesis. This guides attention in the direction of recognized risk factors for schizophrenia affecting initial neurodevelopment at the time of pregnancy. These comprise maternal stress, nutritional deficiencies, maternal infections, intrauterine growth retardation, and complications of pregnancy and birth. However, socio-economic causes, childhood difficulty, and 1st and 2nd generation immigrant background have also been linked with schizophrenia.

Social stressors, for example discrimination or economic hardship, may incline individuals in the direction of delusional or paranoid thinking^[6]. There are also reliable reports of higher prevalence of schizophrenia in individuals born during late winter or in early spring, among individuals born and raised in urban areas, and in subject where the age of the father was relatively old, but also a relationship with young parents has been noticed. The link with advanced paternal age

has been attributed to the amplified amount of *de novo* mutations in their offspring, but different explanations have been suggested. More recently, indication has accumulated associating cannabis use in adolescence, in particular abuse of compounds with high THC content. Likewise, several other influences such as head injury, autoimmune diseases, epilepsy, and severe infections have been related with increased risk^[7].

PATHOPHYSIOLOGY OF SCHIZOPHRENIA

Anatomical Abnormality

Several brain imaging and neuro-pathological studies have tried to relate the signs of schizophrenia to different structure or function of specific brain regions and circuits. There has been advancement in connecting some aspects of the disorder to particular underlying neurobiology and numerous lines of evidence associate the participation of the prefrontal cortex, in specific the cognitive deficits (for example working memory and executive control)^[8].

Nonetheless, delicate reductions in grey matter and irregularities of white matter have been found across many brain areas and circuits. The decrease of grey matter progresses with the period of illness, particularly in the temporal lobe, and seems to be related with antipsychotic treatment. Conversely, even drug-naïve patients display volume decreases (although not as pronounced as treated patients), exclusively in the caudate nucleus and thalamus. Furthermore, in spite of many hundreds of studies, no restricted anatomical or functional abnormalities have been identified that are specific to the disorder.

This is expected to reflect the difficulty and heterogeneity of the psychopathology and related cognitive deficiencies, and the lack of clear margins separating schizophrenia from the other disorders^[8].

Dysfunctional Neurotransmission

There is a logical body of proof from pharmacological and brain imaging literatures associating dysfunction of dopaminergic neurotransmission in the beginning of psychotic symptoms like delusions and hallucinations. Though, while these happen in the majority of cases of schizophrenia, they are also noticed in a range of other psychiatric conditions.

Furthermore, pharmacological, and other, indication indicates that dopaminergic dysfunction is questionable to describe the full range of clinical manifestations of the disorder. Proof from clinical pharmacology, physiology, brain imaging has recommended that disturbed glutamatergic function may add to the biological processes essential some clinical features, in specific cognitive dysfunction^[9]. One notion is that glutamatergic dysfunction in schizophrenia is associated to dysfunction of parvalbumin-positive interneurons inside the cerebral cortex and hippocampus, which are subtle to alterations in NMDA-type glutamate receptors. These fast spiking neurons harmonize the firing of pyramidal neurons and cause the production of gamma oscillations, which is vital to proper cognitive function. Subsequently, dysfunction of this population of neurons may cause the cognitive deficits seen in schizophrenia^[10].

Atypical activity at dopamine receptor sites specifically in D₂ is understood to be linked with many of the symptoms of schizophrenia. Four dopaminergic pathways have been involved:

1. The nigrostriatal pathway initiates in the substantia nigra and finishes in the caudate nucleus. Low dopamine levels inside this pathway are understood to affect the extrapyramidal system, causing motor symptoms^[11].
2. The mesolimbic pathway may play a role in the positive symptoms of schizophrenia in the existence of excess dopamine^[11].
3. Negative symptoms and cognitive deficits in schizophrenia are said to be initiated by low mesocortical dopamine levels^[12].
4. A reduction or blockade of tubero-infundibular dopamine outcomes in elevated prolactin levels resulting in galactorrhea, amenorrhea, and decreased libido^[13].

The serotonin theory for the development of schizophrenia was thought as a result of the detection that lysergic acid diethylamide heightened the effects of serotonin in the brain. Later research led to the formulation of drug compounds that blocked dopamine and serotonin receptors both, unlike older medications, which had effects on dopamine receptors only. The newer drugs were found to be beneficial in relieving the positive as well as negative symptoms of schizophrenia^[12].

Stress-associated Signaling Cascades

Stress-associated signaling cascades are renowned to control the development and maintenance of connectivity of synapses, especially those that involved inflammatory processes and oxidative stress. Microglia involved in synaptic preservation and destruction, specifically synaptic pruning in adolescence, and the major histocompatibility complex I and complement system implying synaptic plasticity are two such examples. Besides, the sharp rise of parvalbumin-positive interneurons which are referred to above the principally vulnerable to oxidative stress can also disrupt appropriate formation and preservation of myelination. Suggestion for the participation of these mechanisms has come from the new studies of preclinical models^[14].

DIAGNOSIS

Schizophrenia is a chronic disorder with several symptoms, where these symptoms are not pathogenic, therefore a diagnosis of schizophrenia is made by a full assessment of patient-specific signs and symptoms, as pronounced in the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5). The DSM-5 mentions that the diagnostic criteria must include the existence of two or more of these active-phase symptoms each remaining for a major portion of minimum one-month duration. The symptoms include delusions, hallucinations, grossly disorganized or catatonic behavior, disorganized speech, and negative symptoms^[2]. At least one of the mentioned symptoms must be disorganized speech, delusions, or hallucinations. Furthermore, the DSM-5 demands that, to confirm a diagnosis of schizophrenia, the patient should also show a reduced level of functioning concerning work, interpersonal relationships, or care of self. There should further be continuous manifestations of schizophrenia for a minimum duration of six months^[15].

An inclusive differential diagnosis of schizophrenia is essential to differentiate the disorder from other mental disorders, for example major depressive disorder with catatonic or psychotic features, or schizoaffective disorder, body dysmorphic disorder, or schizophreniform disorder, and post-traumatic stress disorder, and

also obsessive-compulsive disorder. Hence schizophrenia can be distinguished from these comparable conditions with the help of a careful examination of the duration of the illness, the period of delusions or hallucinations, and the intensity of depressive and manic symptoms. For instance, in the DSM-5, a patient may meet diagnostic criteria for schizophrenia, but does not necessarily meet the 6 month duration of symptoms; therefore a diagnosis of schizophreniform disorder is provisionally made. If symptoms persevere for 6 months a judgment of schizophrenia is made. Additionally, the clinician must approve that the offering symptoms are not due to substance abuse or some other medical condition^[16].

TREATMENT OF SCHIZOPHRENIA

The objectives in treating schizophrenia comprise managing symptoms, avoiding relapse, and growing adaptive functioning so the patient can be assimilated back into the community. As patients seldom come back to their standard level of adaptive functioning, both non-pharmacological and pharmacological managements must be used to enhance long-term results. Pharmacotherapy is the backbone of schizophrenia treatment, but remaining symptoms may continue. For that reason, non-pharmacological treatments, for example psychotherapy, are also vital^[17].

In most schizophrenia patients, it is hard to implement beneficial rehabilitation programs without the help of antipsychotic agents. Quick initiation of drug treatment is important, mainly within five years after the initial acute episode, since that is when most illness-related variations in the brain occur. Predictors of an unfortunate prognosis comprise the illicit use of amphetamines and other stimulants of central nervous system, as well as drug and alcohol abuse. Alcohol, nicotine, and caffeine also have the risk to cause drug interactions^[18].

Pharmacological Therapy

In the occasion of an acute psychotic episode, medication therapy should be administered instantly. During the first seven days of management, the goal is to decrease aggression and to attempt to return the patient to regular functioning (such as sleeping and eating). At the

beginning of treatment, proper dosing must be titrated based on the patient's response^[19].

Treatment through the acute phase of schizophrenia is shadowed by maintenance therapy, which must be intended at increasing socialization and at cultivating self-care and mood. Maintenance therapy is necessary to help avoid relapse. The occurrence of relapse among patients who are on maintenance therapy, versus those not receiving such therapy, is found to be 18% to 32% compared to 60% to 80%, respectively. Drug therapy must be continued for at least one year after the remission of the initial psychotic episode^[20].

Second-generation (atypical) antipsychotics (SGAs)—with the exemption of clozapine—are the drug of choice for first-line management of schizophrenia. Clozapine is not suggested because of its hazard of agranulocytosis. SGAs are typically preferred over the first-generation (typical) antipsychotics (FGAs) since they are associated with rarer extrapyramidal symptoms.^[21] Nevertheless, SGAs demonstrate metabolic side effects, like weight gain, diabetes mellitus, and hyperlipidemia. These adverse effects can add to the augmented risk of cardiovascular mortality perceived in schizophrenia patients^[18].

Combination therapy is suggested only in the later stages of the management algorithm. The prescription of more than two antipsychotics is not advised because it may upsurge the risk of drug interactions, medication errors, and non-adherence^[22]. Before a new antipsychotic agent is started, the patient's whole medication history must be obtained. Whether the patient has presented a favorable or unfavorable reaction to previous antipsychotic treatment will aid the guidance of the selection of a new drug^[18].

Long-Acting Injectable Antipsychotic Agents

Long-acting injectable (LAI) antipsychotic drugs offer a viable opportunity for patients who are non-compliant to an oral medication. Medical staff should regulate whether the patient's non-compliance is due to the adverse effects of management. If so, then the clinician must consider an oral drug with a more favorable side-effect profile. Before transferring to LAI therapy, a small trial should be directed with the oral

equivalent of the LAI to determine acceptability^[23].

A recent meta-analysis of randomized controlled trials (RCTs) decided that results with LAIs are comparable to those with oral antipsychotics. The authors supposed, conversely, that RCTs might not replicate the "real world" effectiveness and safety of LAIs. Consequently, they conducted a meta-analysis of twenty five mirror-image studies, where a total of 5,940 subjects served as their own controls in realistic settings. This analysis established the advantage of LAIs over oral antipsychotics in avoiding hospitalizations (risk ratio [RR] = 0.43) and in dropping the number of hospitalizations (RR = 0.38)^[24].

Treatment-Resistant Schizophrenia

Between 10% and 30% of individuals with schizophrenia display little symptomatic upgrading after multiple trials of FGAs, and an extra 30% to 60% acknowledge partial or insufficient improvement or intolerable side effects during antipsychotic treatment. Clozapine is the most efficient antipsychotic in terms of handling treatment-resistant schizophrenia. This drug is around 30% effective in adjusting schizophrenic episodes in treatment-resistant subjects, equaled with a 4% efficacy amount with the mixture of chlorpromazine and bztropine. Clozapine has also shown to rise serum sodium concentrations in patients with polydipsia and low sodium^[25].

Nevertheless, as indicated earlier, clozapine has a difficult safety profile. For instance, patients treated with this drug are at amplified risk of facing orthostatic hypotension, which can necessitate close monitoring. Furthermore, high-dose clozapine has been related to serious adverse effects like seizures^[26].

Augmentation and Combination Therapy

Both augmentation therapy (medication with ECT or a mood stabilizer) and combination therapy (along with antipsychotics) may be taken in consideration for patients who fail to display a satisfactory response to clozapine. Treating staff should witness the following guidelines while administering augmentation treatment^[27]:

- The therapy must be used only in patients with an insufficient response to preceding therapy.

- Augmentation agents are infrequently operative for schizophrenia symptoms when given alone.
- Patients who respond to augmentation therapy usually improve quickly.
- If an augmentation approach does not help with the patient's symptoms, then the agent must be withdrawn.

Mood stabilizers are frequently used augmentation agents. Lithium, for instance, recovers mood and behavior in some patients but does not possess any antipsychotic effect. In combination treatment, two antipsychotic drugs—FGA and SGA, or two dissimilar SGAs—are administered simultaneously. On the other hand, exposure to various antipsychotics at the same time may intensify the risk of serious side effects^[28].

Mechanism of Action

The specific mechanism of action of antipsychotic drugs is unidentified, even though it has been advocated that these drugs include three main categories^[29]:

- 1) typical, or traditional antipsychotics, which are linked with high dopamine (D₂) antagonism and little serotonin (5-HT_{2A}) antagonism;
 - 2) atypical antipsychotics which have moderate-to-high D₂ antagonism and high 5-HT_{2A} antagonism activity; and
 - 3) atypical antipsychotics that exhibit low D₂ antagonism and great 5-HT_{2A} antagonism.
- 60% to 65% of D₂ receptors need to be engaged to decline the positive symptoms of schizophrenia, while a D₂ blockade rate of 77% or more has been connected with extrapyramidal symptoms.^[30] The enhancement of negative symptoms and cognition with atypical antipsychotics might be due to 5-HT_{2A} antagonism together with D₂ blockade, causing the release of dopamine into the prefrontal cortex. Even though atypical antipsychotics seem to improve negative symptoms, no appropriate treatment options are explicitly indicated for these symptoms^[31].

CONCLUSION

Schizophrenia is a widely prevalent psychiatric disorder, yet much about its etiology and management is unknown. There are several avoidable causes that are identified and several others that are not modifiable. In the recent years many treatment options are emerging where newer drugs and their combination with or without non-

pharmacological therapy has shown promising results. More studies must be done to implement advanced regimens for treatment of schizophrenia.

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