Balancing Therapeutic Safety and Efficacy to Improve Clinical and Economic Outcomes in Schizophrenia: A Clinical Overview

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Abstract

Affecting up to 1% of the global population, schizophrenia is a chronic, disabling psychiatric disorder that has profound effects on patients, families, and caretakers due to its tremendous personal, social, and economic burdens. Schizophrenia commonly presents during late adolescence and early adulthood, and although its onset may be abrupt, the majority of patients experience a slow and gradual development of various clinical signs and symptoms. In addition to psychotic symptoms that may alter one's perception, thoughts, affect, and behavior, schizophrenia is associated with increased morbidity and mortality, reduced life expectancy, and higher risks of homelessness and unemployment. Although much research has been conducted on schizophrenia, the exact etiology of the disease remains unclear and is likely multifactorial, and evidence has suggested that neuroanatomical alterations and neurotransmitter abnormalities contribute to the disease's pathophysiology. It is essential to remember that schizophrenia is a chronic disease that requires long-term treatment. While there are currently no definitive diagnostic tests for schizophrenia, the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* criteria should be used to guide proper diagnosis and identification. Further research and an improved understanding of the pathophysiological basis of schizophrenia may drive more effective treatment options and improved patient outcomes for this complex and challenging disease.

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For author information and disclosures, see end of text.

Schizophrenia is a chronic and disabling psychiatric disorder that commonly presents during late adolescence and early adulthood.[1] Although its prevalence is estimated to be up to 1% of the population worldwide, schizophrenia has profound effects on patients and their families due to the tremendous personal, social, and economic burdens it imposes on these individuals.[2,3] Patients with schizophrenia have a greater likelihood of unemployment and homelessness, and the total economic burden of schizophrenia in the United States is estimated to be approximately $65 billion.[1,3] Much research has been done on schizophrenia, but its exact etiology has yet to be determined and is likely multifactorial.

Epidemiology

The onset of schizophrenia symptoms typically occurs between the late teens and the mid-30s. Patients with disease onset before age 17 years are considered to have early-onset schizophrenia (EOS), and those with onset before age 13 years are considered to have very early–onset schizophrenia (VEOS).[4] The estimated prevalence of VEOS is 1 per 10,000 individuals, and the lifetime prevalence of developing schizophrenia is approximately 0.3% to 0.7%.[4,5] Male patients tend to have an earlier onset of symptoms, between the ages of 15 and 25 years, whereas female patients have later onset, around age 19 to age 35 years. Further, male patients exhibit a higher lifetime risk of developing schizophrenia, with a male-to-female relative risk of about 1.4, and male patients often experience a more severe disease course.[4,6]

Etiology

The exact cause of schizophrenia has yet to be determined, but it is likely heterogeneous and multifactorial.[7] Although most patients with schizophrenia have no family history of psychoses, research in families of patients with schizophrenia has shown that there is likely a genetic component, and the risk of schizophrenia increases as the degree of genetic affinity with

the patient increases. For example, if 1 individual in a pair of twins has schizophrenia, the risk of schizophrenia developing in the other twin is 10% to 15% for dizygotic twins, and increases to 40% to 50% in monozygotic twins.[7] Despite the significant familial risk, however, no genes of large effect have been identified. This pattern could reflect either the epistatic interaction among multiple genes or the contribution of de novo mutations that arise and persist for only 1 or a few generations.[8,9] Rare copy number variants converge, particularly on genes that affect glutamatergic synaptic networks and N-methyl-D-aspartate (NMDA) receptors. Specific genes of interest include NRG1 (neuroregulin 1), DTNBP1 (dysbindin), DRD1-4 (dopamine receptors D1-D4), DISC (disrupted in schizophrenia 1), COMT (catechol-0-methyl-transferase), D-amino acid oxidase (DAAO), D-amino acid oxidase activator (DAOA), and GRM3 (metabotropic glutamate receptor). Despite advances in genetic studies, no particular gene variant has been shown to be sufficient to cause schizophrenia.[7,10]

In epidemiological studies, environmental factors such as urban settings, areas with high rates of migrants, exposure to cannabis during adolescence, and lower socioeconomic class have been linked to the development of schizophrenia. Maternal stress and/or infection (eg, influenza) during pregnancy, nutritional deficiency during the prenatal period, obstetric and perinatal complications (eg, fetal hypoxia), birth during late winter or early spring, and childhood trauma(s) can also increase the risk of development of schizophrenia.[4,7,11] Older paternal age (>45 years) at the time of conception has also been associated with a more than 2-fold increased risk of the offspring developing schizophrenia.[12,13]

Pathophysiology

Neuroanatomical Alterations

Magnetic resonance imaging studies of the brains of patients with schizophrenia have shown reductions in whole brain volume and grey matter volume, and the enlargement of ventricles. Reductions are also seen in temporal lobe areas, such as the hippocampus, amygdala, superior temporal gyri, prefrontal cortex, thalamus, anterior cingulate, and corpus callosum. It has been suggested that disturbances in the development of cerebral asymmetry can contribute to the etiopathogenesis of schizophrenia.[14] Leftward asymmetry of the brain structure may also be reduced in patients with schizophrenia due to a larger right planum temporale compared with normal controls.[14,15] Compared with adults with schizophrenia, patients with EOS appear to have similar brain structural changes, but more severe neuroanatomical alterations.[14,16] The integrity of white matter connections between regions of the brain may also be compromised and lead to impairments, as revealed by diffusion tensor imaging, in such processes as behavioral regulation.[17]

Neurotransmitter Abnormalities

Dopaminergic dysfunction has long been cited as the main cause of schizophrenia symptoms. It has been proposed that patients with schizophrenia have hypoactive mesocortical dopaminergic systems, which are responsible for negative and cognitive symptoms, and hyperactive mesolimbic dopamine systems, which are responsible for the positive symptoms.[14,18] Presynaptic dopamine synthesis and release mechanisms may be most affected; however, dopamine abnormality does not explain all of the symptoms associated with schizophrenia.[11,19] Current antipsychotic medications are effective for many individuals, but nevertheless, a high percentage of patients have no or only partial relief of symptoms, even with the best available agents. Persistent negative and cognitive symptoms are particularly associated with poor outcomes, and do not respond well to existing medications.[11,20]

There is increasing evidence that glutamatergic dysfunction is another possible cause of schizophrenia. The observation that NMDA receptor antagonists, such as phencyclidine and ketamine, can cause clinical symptoms similar to those seen in patients with schizophrenia suggests that schizophrenia may be related to a decrease in NMDA receptor function in the brain.[21-23] More recently, NMDA receptor theories have been supported by the observation that antibodies to NMDA receptors may induce a psychotic state that resembles schizophrenia.[24] As opposed to the dopamine system, which projects preferentially to basal ganglia and frontotemporal regions, the glutamate system is widely distributed throughout the brain and affects sensory regions, as well as those involved in such higher-order processes as memory or executive processing.[23]

Clinical Presentation and Diagnosis

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5),* released in May 2013, provides updated criteria for the diagnosis and classification of various mental disorders, including schizophrenia. For a patient to be appropriately diagnosed with

Table. Symptoms of Schizophrenia[1,11]

Positive	Negative	Cognitive
Hallucination	Apathy	Memory impairment
Delusion	Avolition	Decrease in attention
Disorganized thinking	Alogia	Impaired executive functioning
Suspiciousness	Anhedonia	

schizophrenia, they should exhibit at least 2 Criterion A symptoms for a significant portion of time, defined as a 1-month period or longer, unless successfully treated before this 1-month period has elapsed. Criterion A symptoms include delusions, hallucinations, disorganized speech (eg, frequent derailment or incoherence), grossly disorganized or catatonic behavior, and negative symptoms (ie, diminished emotional expression or avolition). Patients should also show a reduced level of functioning in areas such as self-care, work, and interpersonal relations. Further, some signs of the disturbance, such as mumbling in public, magical thinking, or becoming more withdrawn, must persist for a continuous period of at least 6 months. Differential diagnoses, such as schizoaffective disorder, depressive or bipolar disorder with psychotic features, and psychosis caused by a substance or medical condition should be ruled out.[25]

Compared with *DSM-IV*, in which only 1 Criterion A symptom is required for diagnosis of schizophrenia if the delusions are bizarre (ie, clearly implausible and inconsistent within the culture or from ordinary life experiences) or if hallucinations consist of a voice keeping up a running commentary on the person's behavior or thoughts or consist of 2 or more voices conversing with each other, *DSM-5* requires patients to have 2 or more Criterion A symptoms regardless of the characteristics of the delusions or hallucinations. Other communication disorder of childhood onset was added to Criterion F. Additionally, *DSM-5* does not distinguish the subtypes of schizophrenia, such as paranoid, disorganized, catatonic, undifferentiated, and residual, due to the lack of clinical utility and diagnostic value.[26]

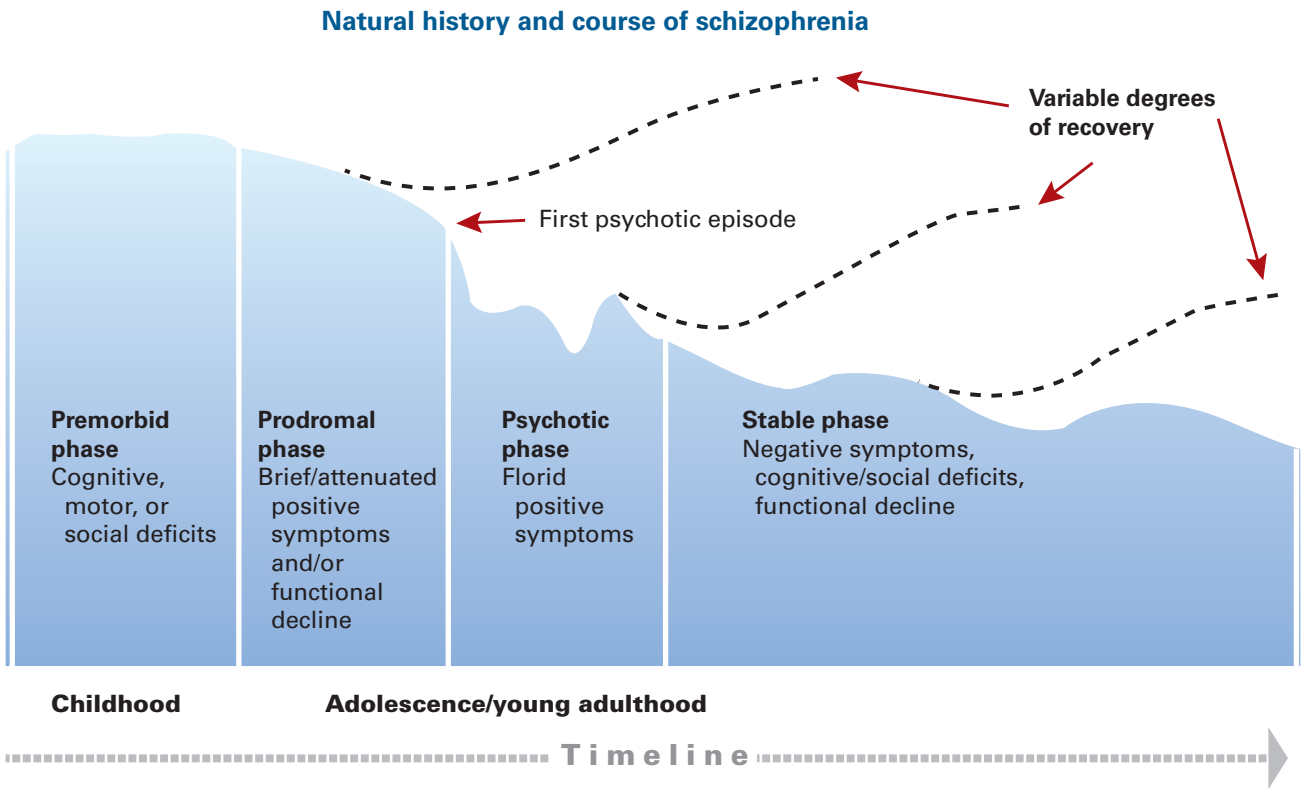
Patients with schizophrenia can present with a wide variety of signs and symptoms, including positive symptoms, negative symptoms, and cognitive impairment (**Table**). Positive symptoms are usually the most recognizable by family and healthcare providers, and include delusions, hallucinations, and paranoia. Persecutory delusions and delusions of reference are the most common types of delusions. Of hallucinations, auditory forms are the most common, but patients may experience hallucinations in other sensory modalities as well. Negative symptoms include the impairment of affective expression, such as apathy (lack of interest), avolition (lack of initiative), alogia (poverty of speech), and anhedonia (inability to experience pleasure). Cognitive impairment includes deficits in information and motor processing speed, decline in verbal and visual memory, and attention deficits.[1] Cognitive impairment is strongly associated with functional disability, as it often leads to poor performance at work or school, the development of social relationship problems, or an inability to live independently.[20,27] In addition to the 3 clusters of symptoms discussed above, patients with schizophrenia often experience depressive symptoms and anxiety.

Clinical Progression

Schizophrenia is a chronic and persistent serious mental illness that requires ongoing treatment.[28] Although disease onset may be abrupt, the majority of patients with schizophrenia have a slow and gradual development of various clinical signs and symptoms. Some patients with schizophrenia may present with a range of developmental, behavioral, emotional, and cognitive impairments during childhood, which is characterized as the premorbid phase (**Figure**). These patients often have delays in motor and language development, reduced attention span, social isolation, and emotional detachment.[1] The prodromal phase often occurs in mid-adolescence, approximately 2 to 3 years before the onset of the first psychotic episode. During the prodromal phase, patients often exhibit subclinical psychotic symptoms, cognitive deficits, negative and mood symptoms, and functional decline.[1,29]

The development of overt psychotic symptoms consistent with Criterion A in the *DSM-5* indicates the formal onset of the first episode of schizophrenia (ie, psychotic phase). Patients usually experience an initial increase in negative and mood symptoms followed by an increase in positive symptoms. Although substance use (ie, substance abuse or dependence) and life stressors have been identified as possible triggers that can precipitate the

Figure. Evolution of Schizophrenia With Phases of Illness[1]



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episode, most patients do not have an identifiable trigger. After the first psychotic break, patients can experience multiple episodes of exacerbations and remissions. Positive symptoms tend to diminish over time, but negative symptoms and cognitive impairment usually persist throughout the patient's lifetime. Functional level tends to decline significantly after the first-break episode, but a plateau in functional impairment is often seen in later life (ie, stabilization phase).[1] Unfortunately, patients with EOS or VEOS often have worse premorbid function, more severe negative and disorganization symptoms, more cognitive deficits, and poorer overall prognosis compared with patients with later-onset schizophrenia.[4]

Additional Clinical Considerations

Mortality

Compared with the general population, the overall mortality rate is increased in patients with schizophrenia, and their lifespan is shortened by approximately 15 to 20 years.[1,30,31] Despite advances in treatment, the relative mortality risk associated with schizophrenia has been increasing over the last 3 decades. Compared with the general population, patients with schizophrenia have 2.5-fold greater risk of dying due to any cause, 12 times the risk of dying of suicide, and a 2- to 3-fold increased risk of death from cardiovascular diseases.[32,33] Whereas suicide has been found to be the leading cause of death in male patients with schizophrenia, cardiovascular disease is the leading cause of death in female patients, and appears to contribute to the largest number of deaths in patients with schizophrenia.[1,34]

Suicide

In patients with schizophrenia, the rate of death by suicide is approximately 5%, and the rate of suicidal attempts ranges between 20% and 40%. Most patients attempt suicide at the initiation of their first treatment trial or during the period before treatment begins.[35] The risk of suicide seems to increase in patients who are male, live alone, have comorbid affective disorders or substance abuse, have a history of suicidal thoughts, and/or demonstrate poor adherence to treatment.[36]

However, patients with protective factors, such as family support and social connectedness, are less likely to attempt suicide. Clozapine is the preferred antipsychotic among patients with suicidality, as it may reduce the risk of suicide.

Medical Comorbidities

Schizophrenia has been associated with an increased risk of developing diabetes and cardiovascular disease; the overall rate of metabolic syndrome in the schizophrenia population was estimated at 32.5%. Female sex, increasing age, second-generation antipsychotic use, and polypharmacy can increase the risk for metabolic syndrome.[37] Studies have shown that, compared with matched healthy control groups, medication-naïve patients with schizophrenia have impaired fasting glucose tolerance; greater insulin resistance; and elevated levels of plasma glucose, insulin, and cortisol.[38,39] Additional risk factors, such as a higher rate of smoking, drug and alcohol use, poor diet, sedentary lifestyle, obesity, dyslipidemia, and cardiac and metabolic adverse effects associated with antipsychotic use, can all contribute to the increased risk for diabetes and cardiovascular disease seen in patients with schizophrenia.[37,40]

Medication Nonadherence

Patient nonadherence is a major concern in the treatment of schizophrenia—the rate of nonadherence has been estimated at 50%. Treatment nonadherence has been associated with increased hospitalization, higher risk of suicide, longer time to remission, poor prognosis, and psychiatric emergencies. The cause of nonadherence is multifactorial; it may be due to poor understanding of the disease, negative attitude toward treatment, concurrent substance use, a poor relationship with the healthcare provider, and/or adverse effects from the medications. Patients with schizophrenia who are male, young, have limited family or social support, and have low socioeconomic backgrounds are more likely to be nonadherent to treatment. To promote adherence, healthcare providers should identify the cause of nonadherence and improve patients' knowledge regarding the disease state. Certain pharmacologic interventions, such as long-acting injectable antipsychotics, can also help to improve treatment adherence and promote constant contact between the patient and the treatment team.[41]

Conclusion

Schizophrenia is a chronic psychiatric disease with multiple etiologies that requires long-term treatment. Although there is no definitive diagnostic test for schizophrenia, clinicians can utilize the criteria listed in *DSM-5* to help guide proper diagnosis and identification. Due to the complex nature of the pathophysiology of schizophrenia and the high level of morbidity and mortality associated with the disease, definitive and effective treatment is urgently needed; however, challenges remain for patients and clinicians alike. Additional research and a better understanding of the pathophysiological basis of schizophrenia will hopefully drive the improvement of treatment options available to patients.

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