Schizophrenia: One Name, Many Different Manifestations

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KEYWORDS

• Schizophrenia • Antipsychotics • Psychopharmacology • Neuropathophysiology
• Psychosis • Dopamine • First episode psychosis

KEY POINTS

- Schizophrenia is a disabling syndrome associated with functional impairment, social isolation, and a decreased life-expectancy.
- Characteristic symptoms include a range of positive, negative, and cognitive psychopathology, with no pathognomonic presentation.
- The etiology of schizophrenia is diverse, and likely includes genetic and environmental risk factors involving distinct neurotransmitters and neurocircuits.
- The pharmacologic treatment of schizophrenia currently consists of postsynaptic dopamine D2 receptor antagonists and can be enhanced by supportive psychosocial interventions.
- New pharmacologic treatments for schizophrenia targeting nondopaminergic receptors are in clinical development.

INTRODUCTION

Schizophrenia is a chronic and debilitating condition with a global prevalence of approximately 1% varying by location and diagnostic criterion.[1,2] The average age of onset is in late adolescence to early twenties in men, and slightly later in women. However, determining the age of onset depends on the recognized symptom, with changes in personality and cognition often occurring before frank psychosis.[3,4] Schizophrenia is associated with considerable morbidity, and is considered one of the top 20 causes of global disability, and the top cause during its acute phase.[5,6]

Although there are effective pharmacologic and supportive psychosocial treatments for schizophrenia, most patients will have an incomplete response to treatment and have residual symptoms.[7] There is often a stepwise decline, especially after episodes of symptom exacerbation, whereby the time to treatment response is variable and

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can take longer to occur after each schizophrenia relapse.[8] Consequently, a key aspect of treatment is enhancing medication adherence and limiting relapse. Continuous treatment has been shown to be more efficacious than intermittent treatment (pharmacologic treatment only being restarted during the first manifestation of acute symptoms).[9]

Schizophrenia is associated with multiple psychosocial sequelae and low rates of functional recovery. Individuals with schizophrenia have high rates of unemployment, homelessness, incarceration, divorce/being unmarried, social isolation, and a decreased overall quality of life.[7] They also report high rates of shame and experiencing stigma.[10] Moreover, the caregivers of those with schizophrenia also report subjective and objective increases in burden and decreases in quality of life.[7,11] Stigmatization and social isolation can also extend to the caregivers which can further exacerbate family burden and reduced quality of life.

Patients diagnosed with schizophrenia have a 2.08 times increased risk of mortality compared with the general population.[12] The life expectancy for individuals with schizophrenia is approximately 15 years less than the general population with the most common cause of death being cardiovascular disease.[13] Individuals with schizophrenia have poor physical health along with low rates of health care utilization, sedentary lifestyles, high rates of nicotine dependence, alcohol use, metabolic syndrome, and obesity.[14] Furthermore, antipsychotic medications, the cornerstone of treatment of schizophrenia, can precipitate and exacerbate metabolic syndrome and weight gain, though studies have also shown that antipsychotic naïve individuals with schizophrenia can also have impaired lipid and glucose regulation. Nearly 1/3 of individuals with schizophrenia will attempt suicide, and 5% will die by suicide.[7,15] Young individuals are at the greatest risk for suicide, with rates 10 times higher than that of the general US population (Standardized mortality ratio: 10.19; 95% confidence interval (CI): 9.29–11.18).[15]

DIAGNOSIS

The diagnosis of schizophrenia is reached after satisfying the criteria in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5-TR).[16] Individuals must have 2 or more of the following symptoms: delusions, hallucinations, disorganized speech, disorganized behavior, and negative symptoms (eg, avolition, anhedonia). Symptoms should be present for at least 1 month, with continuous signs of disturbance for at least 6 months (or less if successfully treated). Additionally, symptoms must be associated with functional impairment.[16] Although the diagnosis can be made using standardized interviewing or scales, such as the Structured Clinical Interview for DSM-5 (SCID-5), clinicians typically assess for schizophrenia by obtaining a comprehensive history, including family history, speaking with collateral sources of information, and conducting a mental status examination.[17,18] Although psychotic symptoms typically result in the patient first receiving medical attention and may be the most concerning and obvious, any symptom can predominate.

Another method of conceptualizing schizophrenia is as a constellation of symptoms with 3 primary domains: (1) positive (eg, delusions, hallucinations, disorganized thought process), (2) negative (eg, apathy, affective flattening, social isolation, anhedonia), and (3) cognitive (eg, memory, executive function). Schizophrenia is heterogeneous. There is no pathognomonic presentation and individual symptoms vary. However, despite a myriad of distinct symptom presentations, pharmacologic treatment is fairly uniform consisting of antipsychotic medications.

Although psychotic symptoms may be the most apparent, they are often preceded by negative and cognitive symptoms in a period known as the psychosis prodrome. The duration of the prodrome varies and can last for months to years, typically characterized

by subtle and gradual changes in behavior, personality, and functioning.[19] However, in other cases, the onset of psychosis can occur abruptly in otherwise highly functioning individuals. Characterizing symptoms is important as positive symptoms are much more amenable to treatment than negative and cognitive symptoms.

At present, there is no blood test for schizophrenia, and as such, schizophrenia is a diagnosis of exclusion. Not all psychosis is schizophrenia, and alternative organic and psychiatric etiologies must be ruled out before a diagnosis of schizophrenia can be reached.[20] A partial list of conditions that can present with symptoms of psychosis is listed in **Table 1**.

ETIOLOGY

The etiology of schizophrenia is unclear and there any many different hypotheses. However, it is likely multifactorial, and as schizophrenia is a heterogeneous condition with different presentations, it is likely that there is more than one cause. Schizophrenia is likely an umbrella concept with multiple distinct conditions and subtypes.[21]

Genetics Versus Environment

Evidence from family, twin, and adoption studies have identified a strong genetic predisposition toward schizophrenia, with heritability ranging from 64% to 81%.[22] Moreover, psychiatric disorders are polygenic, and the family of those with schizophrenia also has an increased risk for manifesting other psychiatric conditions, such as bipolar disorder, major depressive disorder, ADHD, and autism spectrum disorder.[23] Genome-wide association studies have identified that approximately 1/3 of the genetic risk for schizophrenia could be attributed to common genetic variation in over 100 distinct loci which individually contribute small genetic effects.[23,24] Although inheritance is the greatest risk factor, only 1/3 of individuals with schizophrenia have a family history of it. Environmental factors also likely contribute, including male sex, greater paternal age, obstetric and prenatal complications, adverse childhood events,

Table 1
Selected psychiatric and medical causes of psychosis

Psychiatric Conditions	Medical Conditions
Schizoaffective disorder	Delirium
Bipolar disorder	Dementia
Major depressive disorder	Substance abuse
Postpartum depression	Thyroid disorder
Brief psychotic episode	Systemic lupus erythematosus
Schizophreniform disorder	Temporal lobe epilepsy
Delusional disorder	Brain tumor
Obsessive-compulsive disorder	Anti-NMDA receptor encephalitis
Body dysmorphic disorder	Acute intermittent porphyria
Schizotypal personality disorder	Wilson's disease
Borderline personality disorder	Neurosyphilis
Autism spectrum disorder	Vitamin deficiency
	Cushing syndrome
	HIV
	Parkinsons disease
	Multiple sclerosis
	Medication induced
	Traumatic brain injury
	Huntington disease
	Sepsis

immigration, being born or raised in urban areas, and being born in the late-winter to early-spring. Infections have also shown an increased risk, suggesting that the immune system may play a role in the pathogenesis of schizophrenia.[25,26]

Pathophysiology

Historically it was felt that dopaminergic dysfunction resulted in the symptoms of schizophrenia; however, it is likely more complex involving multiple neurotransmitter systems including dopamine, serotonin, and glutamate.

Antipsychotic medications function, in part, by blocking postsynaptic dopamine D2 receptors in the striatum, leading to the hypothesis that dopamine neurotransmitter dysfunction at that location is central to the pathogenesis of schizophrenia. Individuals at: (1) high risk to develop schizophrenia, (2) are in their prodromal phase, (3) are in their first episode of psychosis (FEP), and (4) with chronic schizophrenia have an increased striatal presynaptic dopamine synthesis capacity relative to those without schizophrenia.[27] Administration of dopamimetic agents, such as cocaine and amphetamine, and dopamine precursors such as levodopa, can mimic the positive symptoms of schizophrenia. However, the dopamine hypothesis of schizophrenia is incomplete and does not account for all presentations. Substances that also mimic schizophrenia symptoms are N-methyl-D-aspartate (NMDA) glutamate receptor antagonists, such as dextromethorphan, ketamine, and phencyclidine (PCP), giving credence to the hypofunctioning NMDA receptor hypothesis for schizophrenia, which suggests psychosis is the result of hypofunctioning NMDA receptors on GABA interneurons. Moreover, PCP and ketamine also mimic the negative and cognitive symptoms of schizophrenia, rather than just the positive. Anterior cingulate cortex proton magnetic resonance spectroscopy (^{1}H-MRS) studies and postmortem studies have identified glutamatergic abnormalities in individuals with schizophrenia.[25,28] The hypofunctioning NMDA receptor hypothesis of schizophrenia does not negate the role of dopamine dysfunction in schizophrenia. Dopaminergic hyperactivity is a downstream consequence of glutaminergic dysfunction, resulting in increased dopamine release in the mesolimbic pathway.[29]

In addition to antagonizing dopamine D2 receptors, second-generation antipsychotics (SGAs) also antagonize serotonin 5-HT2a receptors. Overactive 5-HT2a receptors and excess serotonin can result in psychotic symptoms, similar to the psychomimetic effects of 5-HT2a agonists such as LSD and psilocybin. A possible mechanism is that excess serotonin results in the downstream release of glutamate to the ventral tegmental area (VTA), and, analogous to NMDA receptor agonists, causes a further downstream release of mesolimbic dopamine.[29] To support the role of excess serotonin causing psychotic symptoms, pimavanserin, a serotonin 5-HT2a/5-HT2c antagonist/inverse agonist without affinity to the dopamine D2 receptor, treats Parkinson's disease psychosis and is being investigated as a treatment of schizophrenia and Alzheimer's disease psychosis.[30]

Although "all roads may eventually lead to dopamine," there are likely many distinct and interconnected neurotransmitter pathways involving dopamine, glutamate, and serotonin which can result in the symptoms of schizophrenia. It is unlikely that one neurotransmitter is responsible for all schizophrenia presentations, and schizophrenia remains a heterogeneous disorder. Parsing out the etiology of these pathways and individualizing treatment will be a goal of future treatments.

NEUROBIOLOGY OF SCHIZOPHRENIA

No single area of the brain is likely to account for all symptoms of schizophrenia, and several imaging modalities, such as MRI, magnetic resonance spectroscopy (MRS),

positron emission tomography (PET), functional MRI (fMRI), diffusion tensor imaging (DTI), arterial spin labeling (ASL), and neurite orientation dispersion and density imaging (NODDI), among others, have consistently identified abnormalities in brain structure, function, connectivity, and chemistry.[31] Abnormalities are diffuse but are more pronounced in the cortex and subcortical brain regions. Moreover, the origins of these abnormalities have been suggested to occur during early brain development as well as around the time of psychosis onset.[31] Multiple structural abnormalities in schizophrenia have been identified, including (1) smaller hippocampal volumes followed by a smaller amygdala, thalamus, nucleus acumbens, and overall intracranial volume, (2) larger pallidum and lateral ventricle volumes, (3) widespread cortical thinning, (4) gray matter alterations in frontal, temporal, and cingulate cortices, and (5) abnormalities in white matter connections leading to inefficient communication between functional brain regions.[31–33] Additionally, these changes, including decreases in overall brain tissue and gray matter density, may worsen during each psychotic exacerbation. Differences in brain perfusion and metabolism have also been noted in those with schizophrenia in comparison to controls. Individuals with schizophrenia have decreased cerebral blood flow, along with distinct areas of hypoactivation, hyperactivation, and abnormal resting-state brain activity.[31,34] Despite the myriad of reproducible findings, after neuroimaging has ruled out an organic etiology for schizophrenia symptoms, there are few clinical implications for neuroimaging findings at this time. However, neuroimaging has been suggested as an objective biomarker that could one day assist with diagnostic uncertainty and treatment decisions.[35] Biomarkers could also help to predict the risk for developing psychosis in someone that is in their prodromal phase or is at a high risk to develop schizophrenia. Biomarker targets include gray matter loss, NMDA receptor dysconnectivity in the excitatory/inhibitory balance resulting in altered functional network architecture, dopamine hyperactivity, NMDA hypofunction, hippocampal hyperactivity, and autoimmune or neuroinflammation dysregulation.[35]

TREATMENT

Pharmacologic

Efficacy

The mainstay of pharmacologic treatment of schizophrenia consists of first-generation antipsychotic (FGA) and second-generation antipsychotic (SGA) medications. An example of a commonly used FGA is haloperidol, and an example of a commonly used SGA is risperidone. Most antipsychotics are now available as generic medications. Antipsychotic medications have efficacy in treating the positive symptoms of schizophrenia, however, they are less effective at treating negative and cognitive symptoms.[36] Most of the evidence supports continuous treatment with antipsychotic medications as opposed to intermittent treatment which is discontinued on symptomatic remission, though there is debate about this and large studies have attempted to evaluate this question.[37] A meta-analysis of 20 studies showed that the long-term mortality rate is lower in patients with schizophrenia treated with antipsychotic medications in comparison to those who did not use antipsychotic medications.[38] These results were consistent with a nationwide, register-based cohort study of 62,250 patients with schizophrenia, which found long-term antipsychotic use reduced morbidity and all-cause mortality.[39] When factoring in the adverse effects of antipsychotic medications, a critical appraisal of the literature still found that chronic antipsychotic use has a favorable benefit-to-risk ratio, with insufficient evidence to support significant dosage reduction in stabilized patients.[14]

Network meta-analyses of clinical trials of the available antipsychotic medications have established a hierarchy of efficacy: clozapine being superior to olanzapine, risperidone, and amisulpride [not available in US], and in turn potentially superior to all other antipsychotics.[40–42] However, differences in effect size for efficacy outcomes are generally small. Larger differences among the antipsychotics are noted for tolerability outcomes such as drug-induced Parkinsonism, akathisia, sedation/somnolence, weight gain, prolactin elevation, and ECG QTc prolongation. The American Psychiatric Association (APA) Practice Guideline for Schizophrenia recommends routine monitoring for efficacy and tolerability issues, especially early in the course of treatment when an individual is more prone to metabolic, anticholinergic, and motoric side effects.[18]

Considerations regarding the first episode of schizophrenia

Evidence exists that a prolonged duration of untreated psychosis in a person with first-episode psychosis (FEP) is associated lower rates of recovery and a worse response to treatment.[43–45] Fortunately, FEP has a high rate of response to treatment regardless of which antipsychotic medication is selected. In a meta-analysis of antipsychotic medications for the treatment of FEP, few clinically significant differences were found between individual medications. However, haloperidol had higher rates of all-cause discontinuation and was considered to be a suboptimal treatment.[46] SGAs are preferred. Given a similar response to treatment, medication should be selected based on the side-effect profile and dosed conservatively to enhance treatment adherence.

Treatment-refractory schizophrenia

Nearly one-third of individuals with schizophrenia will have an insufficient response to treatment and are considered to have treatment-refractory schizophrenia (TRS).[47] The reasons for this are multifactorial and could be secondary to underlying neurotransmitter abnormalities or different pathophysiological pathways. Before diagnosing a patient with TRS, rule out alternative etiologies, such as pharmacokinetic or pharmacodynamic failures including nonadherence with treatment, active substance abuse, drug–drug interactions, inadequate prior treatments, and subtherapeutic antipsychotic serum levels.[48] A trial of a long-acting injectable antipsychotic will help rule-out “pseudo-resistance” caused by covert nonadherence to oral antipsychotic treatment.[47] After a diagnosis is confirmed, the cornerstone of treatment is clozapine. Clozapine has consistently shown to be the most efficacious antipsychotic for treating TRS, and in addition has potent anti-suicidal and anti-aggressive properties.18 Clozapine dosage and serum level should be optimized, and treatment should persist for at least 12 weeks before deeming treatment failure.[47] Additional guidance is offered regarding safe and optimal titration.[49] If a patient is unable to tolerate clozapine or they show an inadequate response, alternative strategies include: high dose olanzapine, antipsychotic combination therapy, adjunctive medication including mood stabilizers, antidepressants, NMDA receptor modulators, neuromodulation, and psychotherapy, among others.[50,51]

Nonadherence

Despite high morbidity and mortality associated with medication nonadherence, rates of treatment adherence are low in people with schizophrenia. A review of naturalistic studies found rates of nonadherence ranging from approximately 11% to 60%, and another study showed that within 10 days of hospital discharge, up to 25% of patients with schizophrenia were nonadherent.[52,53] Strategies to enhance and monitor adherence include, but are not limited to: psychoeducation, psychotherapy, pill counts, checking medication serum levels, involving support system to remind or administer

medicine, and phone or email reminder systems. Another option is the use of long-acting injectable antipsychotics (LAIs). Although LAIs are typically considered for those with a history of nonadherence, many patients prefer to receive LAIs. The most recent APA schizophrenia practice guideline reflects this, recommending "that patients receive treatment with an LAI if they prefer such treatment or if they have a history of poor or uncertain adherence."[18] Most of the evidence support LAIs in reducing rates of relapse and hospitalization and have also yielded positive results for individuals with FEP or early phase schizophrenia.[54,55] LAIs eliminate the need for daily oral medication and ensures stable serum levels, and using LAIs earlier in the disease course could improve the continuity of treatment.[56] There are several available LAIs with dosing frequency ranging from 2 weeks to 6 months.

New treatments

Despite schizophrenia having many different illness presentations, pharmacologic treatment is fairly uniform consisting today of dopamine receptor antagonists or partial agonists. Negative and cognitive symptoms are typically refractory to existing treatment unless these symptoms are secondary to positive symptoms. However, treatments with alternative mechanisms of action that do not block postsynaptic dopamine receptors are currently in phase 3 of clinical development. These include ulotaront, a trace amine-associated receptor 1 (TAAR1) agonist, and xanomeline-trospium, an M1 and M4 muscarinic cholinergic receptor agonist.[57,58] A glycine transport inhibitor (BI 425809) targeting the NMDA receptor is also being studied for cognitive impairment associated with schizophrenia.[59]

Psychosocial Interventions

In addition to pharmacotherapy, psychosocial treatments are also an integral component of the treatment of schizophrenia and can improve quality of life. This is especially relevant for negative and cognitive symptoms, which are less responsive to pharmacotherapy. Psychosocial interventions can work in tandem with pharmacologic treatments, and can synergistically alleviate symptoms and increase functioning. Psychosocial interventions include, but are not limited to: cognitive remediation and cognitive behavioral therapy, vocational rehabilitation, social skills training, family therapy, individual and family psychoeducation, assertive community treatment (ACT), and case management (also to assist with housing).[60] Psychosocial interventions can start before illness onset in high-risk individuals and may result in improvements in functioning and reduced or delayed risk of transitioning to psychosis.[61] A meta-analysis of psychosocial interventions for relapse prevention in schizophrenia identified family interventions, patient and family psychoeducation, and cognitive behavioral therapy as being especially effective in limiting relapse.[62] However, despite improved outcomes, psychosocial interventions are not available in all regions.

SUMMARY

Schizophrenia is a heterogeneous condition with many different symptomatic presentations. Its etiology is unclear, but likely includes complex genetic and environmental factors. There are multiple different neurotransmitters involved including dopamine, glutamate, and serotonin. It is likely that schizophrenia is an umbrella concept with several different neurobiological causes, and what we consider to be schizophrenia may be several distinct conditions. There are numerous brain changes associated with schizophrenia, including gray matter atrophy and white matter changes. Neuroimaging and neurotransmitter studies could help identify future biomarkers to individualize and guide care. The current medication treatment of schizophrenia consists of

dopamine antagonists, which are reasonably effective at treating the positive symptoms of schizophrenia, but have limited efficacy at treating cognitive and negative symptoms. Common antipsychotic side-effects include metabolic disturbances and movement disorders, and judicious antipsychotic medication selection is warranted. Nondopaminergic medications targeting serotonin, muscarinic, and NMDA receptors are currently under investigation. Psychosocial treatment can be effective in combination with pharmacotherapy and is used to increase overall functioning and patient quality of life. There is a need for new medications with novel mechanisms of action and further research into the diverse etiologies of schizophrenia. Care should be individualized with a focus on improving and maintaining patient quality of life.

CLINICS CARE POINTS

- Individuals with schizophrenia have high rates of unemployment, homelessness, social isolation, and stigma. They can also have low self-esteem.
- The life expectancy for those with schizophrenia is 15 to 20 years less than the general population with high rates of cardiovascular disease; regular follow-up with a primary care provider is recommended.
- Prolonged periods of untreated psychosis are associated with a worse overall prognosis.
- Positive symptoms of schizophrenia are more responsive to treatment than negative and cognitive symptoms.
- A goal of treatment is to enhance medication adherence and limit symptomatic relapse. Continuous treatment with antipsychotic medication is more effective than intermittent treatment. A strategy that has been shown to improve long-term outcomes is long-acting injectable antipsychotics.
- Individuals in their first episode of psychosis have a high rate of response to treatment regardless of which antipsychotic medication is selected. Initial medication selection should be guided by medication side-effect profiles.
- Psychosocial interventions, such as psychotherapy, vocational rehabilitation, and cognitive remediation, can augment treatment response and increase patient overall functioning.

DISCLOSURE

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