Schizophrenia in adults: Epidemiology and pathogenesis

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INTRODUCTION

Schizophrenia is among the most disabling and economically catastrophic medical disorders. It is ranked by the World Health Organization as one of the top 10 illnesses contributing to the global burden of disease [1].

Characteristics of schizophrenia typically include positive symptoms, such as hallucinations and delusions; disorganized behavior; negative symptoms, such as anhedonia, lack of motivation, flat affect, and poverty of speech; and impairments in cognition, including attention, memory, and executive functions. The illness is commonly associated with impairments in social and occupational functioning [2]. Antipsychotic medications are the first-line treatment for schizophrenia. Evidence-based psychosocial interventions in conjunction with pharmacotherapy can help patients achieve recovery.

This topic discusses the epidemiology and pathogenesis of schizophrenia. Clinical manifestations, assessment, diagnosis, and course of schizophrenia are discussed separately. Anxiety and depression in schizophrenia are discussed separately. Psychosocial and pharmacologic treatments for schizophrenia are discussed separately, including long-acting antipsychotics, clozapine, and management of antipsychotic side effects. Evaluation and management of treatment resistant schizophrenia are also reviewed separately.

- (See "Schizophrenia in adults: Clinical features, assessment, and diagnosis".)
- (See "Schizophrenia in adults: Maintenance therapy and side effect management".)

- (See "Schizophrenia in adults: Pharmacotherapy with long-acting injectable antipsychotic medication".)
- (See "Schizophrenia in adults: Psychosocial management".)
- (See "Depression in schizophrenia".)
- (See "Anxiety in schizophrenia".)
- (See "Evaluation and management of treatment-resistant schizophrenia".)

EPIDEMIOLOGY

Schizophrenia occurs throughout the world. The prevalence of schizophrenia (ie, the number of cases in a population at any one time point) approaches 1 percent internationally. The incidence (the number of new cases annually) is approximately 1.5 per 10,000 people [3]. Age of onset is typically during adolescence; childhood and late-life onset (over 45 years) are less common. Slightly more men are diagnosed with schizophrenia than women (on the order of 1.4:1) [4], and women tend to be diagnosed later in life than men. Modal age of onset is between 18 and 25 for men and between 25 and 35 for women, with a second peak occurring around menopause [5]. There is also some indication that the prognosis is worse in men [6,7].

Co-occurring conditions — People with schizophrenia have higher rates of several psychiatric disorders than people without schizophrenia, including:

- Depressive disorders (see "Depression in schizophrenia")
- Anxiety disorders: social anxiety disorder, posttraumatic stress disorder, and obsessive-compulsive disorder (see "Anxiety in schizophrenia")
- Alcohol and other substance use disorders (see "Co-occurring schizophrenia and substance use disorder: Epidemiology, pathogenesis, clinical manifestations, course, assessment and diagnosis")

People with schizophrenia are also at greater risk for co-occurring conditions, such as metabolic and neurologic problems. (See "Schizophrenia in adults: Clinical features, assessment, and diagnosis", section on 'Associated physical manifestations'.)

Risk factors — A number of epidemiological risk factors have been associated with the development of schizophrenia [8], including:

- Living in an urban area [9,10]
- Immigration [11,12]

- Obstetrical complications [13]
- Late winter-early spring birth – Perhaps reflecting exposure to influenza virus during neural development
- Advanced paternal age at conception [14] – May be associated with an increased risk of de novo mutations [15]
- Cannabis use and cigarette smoking [16,17]
- Childhood adversity [18]

Environmental risk factors for schizophrenia are discussed below. (See 'External factors' below.)

Cost — The cost of schizophrenia is staggering. The overall cost of schizophrenia in the United States in 2002 was estimated at approximately $63 billion [19]. This figure includes direct health care costs and indirect costs associated with loss of productivity. A study comparing the cost of schizophrenia in India in 2001 with the cost in the same catchment area in 2011 found that the cost had doubled in those 10 years, mainly related to increases in indirect costs [20]. A study examining United States insurance claims found that the annual health-related expenses of someone with chronic schizophrenia averaged more than $15,000 [21]. The cost of schizophrenia treatment from 2004 to 2009 to Medicare in the United States increased from $9.4 billion to $11.5 billion [22].

Deficit schizophrenia — Deficit schizophrenia, characterized by primary, enduring negative symptoms, seems to be a specific disease process within the larger syndrome of schizophrenia. Approximately 15 to 20 percent of the total schizophrenia population has the deficit form of schizophrenia [23-26]. They are more likely to be male and more likely to have relatives with schizophrenia than people with nondeficit schizophrenia [27-31]. As opposed to the excess of late winter-early spring births observed in schizophrenia in general, there is a disproportionate rate of summer births in the deficit group [23,32]. Examples of negative symptoms include anhedonia, asociality, blunted affect, lack of motivation, and poverty of speech. People with deficit schizophrenia are less likely to have co-occurring substance misuse disorders, depression, suicidal ideation and behavior, or delusions with high emotional content (such as jealous delusions) compared to nondeficit schizophrenia [33-35]. (See "Schizophrenia in adults: Clinical features, assessment, and diagnosis", section on 'Negative symptoms'.)

PATHOGENESIS

Although the pathogenesis of the disorder is unknown, it is almost certain that schizophrenia represents a syndrome comprised of multiple diseases that present with similar signs and symptoms [36]. This heterogeneity complicates the elucidation of the etiological and pathophysiological factors that underlie the group of disorders. In addition, schizophrenia appears to be a uniquely human condition, which limits the utility of animal models and further complicates the elucidation of the etiopathophysiology of the disorder [37].

Genetic and external factors — There is considerable evidence to suggest that the pathophysiology of schizophrenia proceeds from a complex interaction between genes and the environment, which complicates efforts to differentiate the relative contributions of genetic from environmental risk factors. For example, environmental factors can influence gene expression just as a person's genetic make-up can influence response to environmental stressors.

The result of the interplay between genetic and external risk factors is disruption of neural circuit and neurotransmitter system function. (See 'Neurodevelopment, neuropathology, and vulnerabilities' below and 'Neurotransmitters' below.)

Genetic factors — Twin studies were the first studies to provide compelling evidence for the role of genetic factors in the etiology of schizophrenia. These studies were conducted in monozygotic and dizygotic twins to examine the concordance rates of schizophrenia within the twin pairs. The observed concordance rate in monozygotic twins, who share 100 percent of their genes, is approximately 40 to 50 percent, whereas the observed concordance rate in dizygotic twins, who share 50 percent of their genes, is approximately 10 to 15 percent. [37-39]. The increased concordance rate of schizophrenia in monozygotic compared to dizygotic twins suggests a strong genetic component to schizophrenia. The offspring of the unaffected monozygotic twins are at increased risk of schizophrenia, which further supports the existence of a genetic predisposition for the illness. The fact that the monozygotic twin concordance rate is less than 100 percent, however, suggests that nongenetic, environmental factors are also involved in the development of the illness [37-39]. Adoption studies have provided further evidence for the presence of genetic risk factors.

Although there is abundant evidence for genetic risk factors, the specific genes involved in the etiology of schizophrenia have not been identified. Initial studies have used genetic linkage or candidate gene approaches to identify several specific genes as candidates for a role in the development of schizophrenia (table 1).

The mapping of the human genome has allowed for the study of associations between gene variants and risk or occurrence of diseases, ie, genome-wide association studies (GWAS). The

results of GWAS of schizophrenia support a polygenic model, in which multiple genes with additive small effects lead to the disorder. As many as 500,000 single nucleotide polymorphisms (SNPs) have been tested in GWAS for association with schizophrenia. In a study of over 35,000 cases and 110,000 controls, 108 SNPs were found to have a significant association with schizophrenia [40]. The identified genetic loci supported the involvement of the dopaminergic and glutamatergic neurotransmitter systems in the pathophysiology of schizophrenia. The study also replicated previous studies that have shown an association between genes of the major histocompatibility complex (MHC), which support immune functions, and schizophrenia. A 2016 study of the MHC locus demonstrated that expression of complement component 4 allele A (C4A) was proportional to the risk of having schizophrenia [41]. C4 expression and activity were then tested in mouse models and shown to be related to adolescent pruning of brain synapses. These findings are consistent with decreased “neuropil,” or dendritic density, which has been reliably observed in people with schizophrenia [42]. In the largest GWAS of schizophrenia (76,755 cases and 243,649 controls), 287 SNPs were found to have a significant association with schizophrenia, with multiple SNPs related to genes that are implicated in synaptic biology [43]. (See "Genetic association and GWAS studies: Principles and applications".)

Another attempt to delineate the genetics of schizophrenia is the evaluation of copy number variants (CNVs), which are genes that have been duplicated or deleted. People with schizophrenia have been found to have higher rates of CNVs. The most frequent CNV associated with schizophrenia is a deletion on the long arm of chromosome 22 (22q11) [44]. (See "Genetic association and GWAS studies: Principles and applications".)

Finally, there has been considerable interest in the potential role that epigenetics may play in the etiology of schizophrenia [45]. Epigenetics refers to the chemical modification of DNA and histones, the proteins that are involved in the packaging of DNA in the nucleus. These epigenetic modifications are of particular interest in schizophrenia, since they provide a mechanism for the translation of environmental risk factors into altered gene function. There have been several small sample studies conducted in people with a first episode of psychosis [46]. These studies provide evidence for epigenetic alterations in schizophrenia, but they have not been able to demonstrate a consistent set of abnormalities [46].

External factors

Obstetrical complications — Various perinatal problems, grouped together for analysis as “obstetrical complications,” increase the risk of later development of schizophrenia two-fold [13]. These perinatal problems include:

- Hemorrhage

- Preterm labor
- Blood-group incompatibilities
- Fetal hypoxia
- Maternal infection (see 'Infections' below)

The accuracy of these data, based on maternal recall many years after childbirth, has been questioned, but studies suggest that the risk does not appear to be influenced by inaccurate memories [47,48]. The association between obstetrical complications and the development of schizophrenia has also been observed in data from medical records, which do not rely on recall [13]. The presence of obstetrical complications may interact with genetic risk for the illness, such that the liability for schizophrenia explained by genetic factors is significantly greater in the offspring of women who had perinatal complications, than those who did not [49].

In studies based on subsequent hospital records, pregnancy during famines in the Netherlands (1944 through 1945) [50] and in China (1959 through 1961) [51,52] has been associated with a two-fold risk of schizophrenia in the offspring. The results of these studies indicate that maternal nutrition is a critical factor in the development of schizophrenia. Other, related factors associated with an increased risk of subsequently developing schizophrenia include being the product of an unwanted pregnancy [53] and the prenatal death of the father [54].

Increased prenatal maternal stress has been proposed as the common pathophysiological mechanism underlying risk factors, such as famine, bereavement, and antenatal infection. An animal model provides some support for this theory [55].

Infections — Several epidemiological findings have suggested a possible role of certain infectious agents as potential risk factors for the development of schizophrenia:

- Numerous epidemiological studies have found an increase in schizophrenia prevalence in cohorts born during influenza epidemics [56].
    - The increased risk for schizophrenia among those born in the late winter-early spring could possibly reflect increased maternal exposure to influenza virus during prenatal neural development.
- High maternal IgG antibodies to the parasite toxoplasma gondii have been found to increase the relative risk of developing schizophrenia in offspring by approximately 60 to 70 percent [57,58].
- Studies have varied on whether herpes simplex virus type 2 maternal infection increases the risk for schizophrenia; some studies have found increased risks between 60 percent to

more than 400 percent [59,60], while other studies have found no increased risk [61].

- Other infectious agents associated with schizophrenia appear to have an influence outside the model of perinatal exposure of the affected individual. As examples:
  - Higher maternal levels of IgG to toxoplasma gondii are related to the later development of schizophrenia in the mother herself [62].
  - Measles antibodies are higher in people with schizophrenia, especially in those with recent-onset of psychosis, than controls [63].
  - Bacterial infections during childhood, which lead to hospitalization, are related to an increased risk for developing schizophrenia [64,65].

The mechanism by which infections increase the risk of schizophrenia is unclear. There is little evidence to suggest that the risk is associated with direct damage by the infectious agent to the central nervous system (CNS). A study comparing individuals hospitalized for meningitis as children to a control group who were hospitalized with gastroenteritis as children found no difference in the risk of later hospitalization for schizophrenia [66]. A more likely explanation is that infection by certain agents triggers an immune response in a mother that is passed through the placenta to the developing fetus, which compromises the blood brain barrier and allows antibodies, which cross-react with CNS proteins, to enter into the developing nervous system [67]. Early childhood infections could also initiate an immune response and lead to a general state of increased inflammation. (See 'Inflammation' below.)

Inflammation — Increased immune system activation leads to higher levels of circulating pro-inflammatory cytokines. Increased pro-inflammatory cytokine levels have been frequently observed in schizophrenia [68]. Cytokines can alter the blood-brain barrier, or be produced locally in the CNS by activated microglia, and may be responsible for psychosis, its exacerbation, or cognitive impairments [69]. The actions of antipsychotic drugs may be partially mediated by the anti-inflammatory effects of these agents [70].

In addition to associations between schizophrenia and some infections, there is other evidence for abnormal immune activation in people with schizophrenia. (See 'Infections' above.)

Autoimmune disorders that have been associated with a higher prevalence of schizophrenia include [71,72]:

- Acquired hemolytic anemia
- Bullous pemphigoid
- Celiac disease

- Interstitial cystitis
- Thyrotoxicosis

(A notable exception is rheumatoid arthritis, in which schizophrenia rates are lower than expected based on rates in the general population [73]. People with schizophrenia are also more likely to have circulating antibodies to proteins common in most Western diets, such as gluten [74,75] and casein [76,77].)

Clinical trials of anti-inflammatory agents for psychosis have been spurred, in part, by these findings.

Inflammation in people with schizophrenia may also be responsible for some of the disorder's associated conditions such as heart disease (through decreased elasticity of inflamed blood vessels) and diabetes (See "Schizophrenia in adults: Clinical features, assessment, and diagnosis", section on 'Metabolic disturbances'.)

Cannabis use — Epidemiological studies suggest that cannabis use is a risk factor for the development of psychosis [78-85]. The increased risk posed by cannabis use depends on other risk factors, such as family history. In contrast to the psychotomimetic properties of delta-9-tetrahydrocannabinol (THC), the cannabis ingredient cannabidiol (CBD) has been shown to attenuate psychotic symptoms [86,87]. The mechanism by which CBD exerts this potential effect is unknown. (See "Cannabis use and disorder: Epidemiology, pharmacology, comorbidities, and adverse effects", section on 'Psychiatric effects'.)

Cigarette smoking — Cigarette smoking has been associated with schizophrenia. Smoking may confer a risk of developing schizophrenia or there may be a common, underlying risk factor for both the development of schizophrenia and smoking. In a prospective study including over 900,000 individuals, the incidence of newly diagnosed schizophrenia (or nonaffective psychosis) was higher in smokers than in nonsmokers (adjusted incidence rate ratio 3.32, 95% CI 2.67-4.14 in males and 2.13, 95% CI 1.76-2.57 in females) [88]. The risk was found to be dose dependent, with individuals identifying as heavy smokers at greater risk of diagnosis with schizophrenia than those identifying as moderate or light smokers.

Studies of the effect of cigarette smoking during pregnancy on the risk for the development of schizophrenia have been mixed. The first study to use serum cotinine as a biomarker for smoking, however, found cigarette smoking during pregnancy significantly increases the odds of schizophrenia in the offspring (odds ratio 3.41, 95% CI 1.86-6.24). This study was based on a Finnish national health registry and included 977 cases of schizophrenia [89].

Although this finding could be related to nicotinic acetylcholine perturbations during development or fetal hypoxia, it may simply reflect genetic risk. It is well known that first-degree relatives of people with schizophrenia have higher rates of smoking compared with the relatives of healthy controls [90].

Immigration — Numerous studies in multiple countries have observed a higher prevalence of schizophrenia in immigrant populations compared with native-born populations [11,12]. This increased relative risk can be as high as four-fold, depending on the study. An increased risk appears to extend to second-generation immigrants as well [12].

Several possible explanations for the association between immigrants and schizophrenia have been proposed:

- Schizophrenia may be overdiagnosed in immigrant populations; however, further research suggests that this cannot entirely explain the increase in risk observed [91].

- In people with either a genetic or neurodevelopmental biological risk for schizophrenia, stress can play a role in the ultimate development of the disorder. In this way, the stress of immigration, becoming part of an outsider group, may contribute to the development of schizophrenia. Studies have found associations between the amount of social discrimination experienced by immigrant groups and the rates of schizophrenia in the group; that is, immigrant groups experiencing more discrimination have higher rates of schizophrenia than immigrant groups experiencing lower rates of social discrimination. This finding has been observed in several immigrant groups in several countries:

  - Ethiopian immigrants to Israel [92]
  - Moroccan immigrants to the Netherlands [12]
  - Caribbean immigrants to the United Kingdom [93]

- The increased risk of schizophrenia in immigrants may be related to vitamin D deficiency, especially among individuals who move to more northern latitudes [94].

Childhood adversity — Childhood adversity includes physical, psychological or sexual abuse and parental separation [8]. In a meta-analysis of 36 cross-sectional and prospective studies, childhood adversities were found to be significantly related to the occurrence of positive psychotic symptoms or a mental illness with psychosis, including schizophrenia (odds ratio 2.8). The estimated population attributable risk was 33 percent [18].

Neurodevelopment, neuropathology, and vulnerabilities — Schizophrenia is a neurodevelopmental disorder with neuropathological changes that may begin in utero [95].

Brain morphology and neuropathology — Studies including people with prodromal symptoms or a first episode of psychosis have shown reductions in gray matter volumes in multiple brain regions, including prefrontal, and superior and medial temporal lobes [96]. The neuroanatomical changes in the early stages of psychosis appear beyond those associated with normal development [97].

Increasing evidence suggests that the neuropathological changes in the prodrome and first episode of psychosis are dynamic and may differ from what is observed in the more chronic forms of the illness. This neuroplasticity in early psychosis may offer a window of opportunity to alter the course of the illness.

Vulnerability to insults — Pre- or perinatal neurodevelopmental abnormalities are likely to lead to a vulnerability to postpubertal insults that contribute to the accelerated loss of gray matter and aberrant connectivity in the cortical regions of vulnerable individuals. Additionally, external factors, such as substance use, stress, and maternal infection, may contribute to the pathophysiological process(es) [97-99]. (See 'External factors' above.)

While disturbances of neurodevelopment early in life may be necessary for the future emergence of the illness, environmental influences during the late adolescent period may contribute to the emergence of a first episode of psychosis via a range of possible interconnected neuropathological mechanisms. Examples of this include: increased hypothalamic pituitary axis activity, N-methyl-D-aspartate receptor hypofunction, glutamatergic or dopaminergic transmission abnormalities, reduced neuroplasticity, and neuroinflammation [100].

Hypofrontality/brain glucose metabolism — Decreased glucose metabolism, particularly in the frontal cortex, may be a contributing factor to the pathophysiology of schizophrenia. Hypofrontality is theorized to be related to the negative and cognitive symptoms that are pervasive and often refractory to treatment in schizophrenia. In a meta-analysis of 36 studies including 1335 participants, regional brain glucose metabolism in participants with schizophrenia were compared to healthy controls [101]. Frontal absolute glucose metabolism and metabolism relative to whole brain were lower in participants with chronic schizophrenia than controls or those with first episode of psychosis, with differences most pronounced in the medicated participants with schizophrenia. Differences were not found in parietal, temporal, occipital lobe, or thalamic metabolism in participants with schizophrenia versus controls. Although this meta-analysis could not determine whether the decreased glucose metabolism observed in the frontal cortex of people with schizophrenia is a result of chronic illness, a cause of chronic illness, or whether it is related to medication exposure, it supports a relationship between hypofrontality and schizophrenia.

Neurotransmitters

Dopamine — The vast majority of drugs with antipsychotic properties block the dopaminergic D2 receptor, a finding that has led to the dopamine hypothesis of schizophrenia, in which excess dopamine in the mesolimbic tract has been hypothesized to cause positive psychotic symptoms. The mechanisms that underlie this alteration in dopamine activity has been the focus of considerable study. Research suggests that decreased activity of the presynaptic D2 autoreceptor may represent the underlying cause of the excess mesolimbic dopamine [102].

However, if dopamine were the sole neurotransmitter disrupted in schizophrenia, then antipsychotics would be universally and completely effective for these symptoms, but, despite adequate antipsychotic treatment, many people with schizophrenia continue to exhibit positive symptoms. Therefore, it is likely that dysfunction in other neurotransmitter systems is required to explain why many people with the illness exhibit only a partial reduction in positive symptoms, and why clozapine, the most efficacious antipsychotic in schizophrenia, is a weak D2 antagonist.

Decreased dopamine in the prefrontal cortex (largely affecting the D1 receptor) may be responsible for some of the cognitive and negative symptoms observed in schizophrenia [103,104]. (See "Schizophrenia in adults: Clinical features, assessment, and diagnosis", section on 'Clinical manifestations'.)

Glutamate — Glutamate is the major CNS excitatory neurotransmitter. Hypofunction of the N-methyl-D-aspartate (NMDA) glutamate receptor has been hypothesized to contribute to the pathology of schizophrenia [105]. Evidence comes from:

- Clinical observations of people who have misused phencyclidine (a NMDA receptor antagonist)
- Challenge studies using ketamine (a NMDA receptor antagonist) [106-108]
- Genetic findings [105]
- Postmortem studies [109]
- Studies measuring the levels of endogenous NMDA receptor agonists and antagonists in the CNS of people with schizophrenia [110-112]
- Magnetic resonance spectroscopy studies [113]

Clinical trials with agents that enhance glutamatergic neurotransmission have had varied results depending on the mechanism of the agent used [114,115]. (See "Schizophrenia in adults: Maintenance therapy and side effect management".)

Gamma-amino-butyric acid — Gamma-aminobutyric acid (GABA) is the major CNS inhibitory neurotransmitter. GABAergic interneurons are important for regulation of prefrontal cortical function, through their modulation of glutamatergic pyramidal cells. Several lines of evidence suggest that these interneurons are dysfunctional in people with schizophrenia [112,116-121].

- Postmortem studies in people with schizophrenia have found decreased levels of glutamic acid decarboxylase (GAD67) mRNA expression in the prefrontal cortex [122].
- In people with schizophrenia with decreased GAD67, there is a decrease in the density of chandelier cell connections with the pyramidal cell axon initial segment [122] and in the immunoreactivity of the GABA plasma membrane transporter-1 in chandelier cell axon terminals [122].
- There appears to be a decrease in GABA reuptake transporter mRNA levels [122] and an increase in GABAA alpha-2 subunit density on the axon initial segment [122], both of which may be compensatory shifts.

Acetylcholine — The observation of increased smoking behaviors in people with schizophrenia [123-126] led to the hypothesis that nicotine, which stimulates a subset of acetylcholine receptors, is correcting a fundamental neurochemical problem in schizophrenia. Treatment with nicotine or a nicotinic cholinergic drug can normalize some eye-tracking and EEG abnormalities observed in people with schizophrenia [127-131] and may acutely improve some aspects of cognition [132,133]. However, nicotinic acetylcholine receptors can affect many other neurotransmitter systems (for example, nicotine can enhance current mediated by glutamate receptors in dopamine neurons of the rat ventral tegmentum [134,135]), and so it is not clear whether the cholinergic system is primarily disrupted in schizophrenia or the disruption is secondary to other pathological characteristics of the illness.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Psychotic disorders".)

SUMMARY AND RECOMMENDATIONS

- **Schizophrenia** – Schizophrenia is among the most disabling and economically catastrophic medical disorders. Characteristic manifestations of schizophrenia typically include positive symptoms; disorganized speech; negative symptoms; and impairments in cognition. The illness is commonly associated with impaired social and occupational functioning. (See 'Introduction' above.)

- **Epidemiology** – Schizophrenia has a worldwide prevalence approaching 1 percent, with an incidence of approximately 1.5 new cases annually per 10,000 people. (See 'Epidemiology' above.)

- **Co-occurring conditions** – Individuals with schizophrenia have higher rates of co-occurring depression, anxiety disorders, substance use disorders, and suicidal ideation and behavior compared to people without schizophrenia. (See 'Co-occurring conditions' above.)

- **Deficit schizophrenia** – Approximately 15 to 20 percent of individuals with schizophrenia have the deficit form of schizophrenia, characterized by primary, enduring negative symptoms. (See 'Deficit schizophrenia' above and "Schizophrenia in adults: Clinical features, assessment, and diagnosis", section on 'Negative symptoms'.)

- **Pathogenesis** – Although the pathogenesis of the disorder is unknown, schizophrenia is likely a heterogeneous syndrome comprised of multiple diseases that present with similar signs and symptoms. The disorder appears to proceed from a complex interaction between genes and external/environmental factors. (See 'Pathogenesis' above.)

  - **External factors** – Obstetrical complications, perinatal infection, inflammation, cannabis use, tobacco use, immigration and childhood adversities appear to play a role in the development of schizophrenia. (See 'External factors' above.)

  - **Neurodevelopment, neuropathology, and vulnerabilities** – Schizophrenia is a neurodevelopmental disorder with neuropathological changes that may begin in utero. (See 'Neurodevelopment, neuropathology, and vulnerabilities' above.)

  - **Neurotransmitters** – Several neurotransmitter systems are involved in the pathology of schizophrenia including dopamine, glutamate, gamma-aminobutyric acid, and acetylcholine. These represent the current best targets for pharmacologic intervention in the disorder. (See 'Neurotransmitters' above.)

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