Berkeley Pharma Tech
Journal of Medicine

Preventing Schizophrenia: Insights from Epigenetic Research

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Keywords:
Epienetics
Schizophrenia
Prodrome
Psychosis

Abstract

Schizophrenia is a neurological disorder that affects an individual's perception of themselves and the world around them. In recent years, research on schizophrenia has plateaued, with much of the focus placed on post-onset treatments, such as the use of antipsychotic medications and psychotherapy. Although the disorder has been extensively studied, the prodromal stage—preceding the onset of psychosis—remains relatively underexplored. We assert in this scientific review that the prodromal stage offers significant promise in the prevention or strong reduction of schizophrenic symptoms and has been overlooked by previous research. Emerging studies suggest that both pharmacological and psychological interventions targeting epigenetic markers may offer promising new approaches for early-stage treatment.

Published July 31, 2025

Full Open Access

1. Introduction

Schizophrenia is a highly debilitating neurodevelopmental disorder that significantly affects an individual's mental health, cognition, and behavior. Affecting nearly one percent of the U.S. population, the disorder currently has no known cure. Most research to date has focused on alleviating the severity of symptoms following the onset and formal diagnosis. Common symptoms of schizophrenia include hallucinations, delusions, and disorganized thinking, speech, and movement.[1]

1.1 Background on Schizophrenia

Globally, schizophrenia affects approximately 0.32% of the population—about 1 in 300 individuals. The disorder also exhibits a strong hereditary component, with genetic studies suggesting up to a 90% likelihood of heritability from one generation to the next. Schizophrenic symptoms are generally categorized into two broad groups: positive and negative symptoms. Both types are detrimental to an individual's functioning and tend to worsen over time.[1]

Positive symptoms are any change in behavior or thought that was not originally present. These include delusions, hallucinations, confused thinking, and confused speech. These symptoms can be managed by antipsychotic medications. On the contrary, negative symptoms are classified as a withdrawal from the world. Individuals with Schizophrenia experiencing these symptoms take no interest in the things they used to care about and essentially appear emotionless. Examples of these symptoms include apathy, little emotion, poor attention and concentration, and depression. Unlike positive symptoms, negative symptoms are more resistant to pharmacological treatment and often emerge months or even years before positive symptoms, making early detection and intervention particularly challenging.[1]

1.2 Clinical Overview of Schizophrenia

Schizophrenia is a chronic disorder that affects both men and women equally. As of 2022, it is estimated to impact around 1 in 222 adults globally.[1] The typical age of onset falls within early adulthood, generally

between the late teens and early thirties, with men tending to exhibit symptoms earlier than women. While childhood-onset schizophrenia is rare, cases have been documented in individuals as young as thirteen.[2]

Schizophrenic symptoms can range in severity from mild to disabling and are typically classified into three categories: positive, negative, and cognitive. Positive symptoms reflect the presence of abnormal thoughts or behaviors, such as auditory or visual hallucinations, persistent delusions, disorganized thinking, and incoherent speech. Negative symptoms represent a reduction or absence of normal emotional and behavioral functions. These include diminished motivation, anhedonia (lack of pleasure), flat affect, limited vocabulary and speech detail, and social withdrawal. Cognitive symptoms involve deficits in attention, memory, and executive functioning, which can impair decision-making, judgment, and problem-solving abilities.[2]

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), a diagnosis of schizophrenia requires the presence of at least two of the following symptoms for a significant duration: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms. Crucially, at least one of the symptoms must be delusions, hallucinations, or disorganized speech. Additionally, other psychotic or schizotypal disorders must be ruled out in the diagnostic process.[2] If left untreated, patients with schizophrenia may suffer psychological distress, relationship difficulties, employment issues, struggle with substance abuse, and self-harm. Schizophrenia is further associated with a variety of comorbidities, the most common of which being comorbid substance abuse and depression in about half of individuals with the condition.[3] Additional psychiatric comorbidities include PTSD, OCD, and panic disorder. The addition of these psychiatric conditions can greatly hinder the proper diagnosis, and treatment of schizophrenia. This can be due to the possibility of an individual's symptoms having crossover from both conditions, meaning it can be hard to pinpoint whether the individual has both conditions at the same time. Furthermore, there could be different medicinal treatment methods for schizophrenia and an additional condition that may have conflicts.[3]

The timeline of schizophrenia development has been insufficiently studied, largely due to the challenges in accurately identifying and tracking the early progression of symptoms. While a subset of individuals experience an acute onset of the disorder, approximately three out of four cases are preceded by a prodromal phase.[4] This phase varies in duration but typically lasts between one and five years. During the prodrome, negative symptoms and some cognitive impairments often begin to emerge. In some cases, a first-episode psychosis (FEP) may occur later in the prodromal period, following the appearance of mild psychotic symptoms.

During this phase, individuals might experience subtle changes in perception, thought patterns, or behavior that can precede the onset of more severe psychotic symptoms, such as delusions or hallucinations. Recognizing and understanding these early signs can be crucial for timely intervention and treatment. This is particularly relevant for clinical high-risk (CHR) individuals, who exhibit early signs or symptoms indicating a heightened likelihood of developing a psychotic disorder, such as schizophrenia, in the future. Several screening tools have been developed to identify CHR individuals, with varying degrees of success. The Early Detection, Intervention, and Prevention of Psychosis Program (EDIPPP) employed the Structured Interview for Prodromal Syndromes (SIPS) in conjunction with the Scale of Prodromal Symptoms (SOPS) to detect early signs of psychosis with notable accuracy.[5] The Positive and Negative Syndrome Scale (PANSS), the Basel Screening Instrument for Psychosis (BSIP)[6], and the Comprehensive Assessment of the At-Risk Mental State (CAARMS)[7] have all proven to have valid and reliable methods of screening for individuals at risk for psychosis. However, despite the efficacy of these tools in detecting prodromal symptoms, their ability to accurately predict progression to a full psychotic disorder remains limited. This raises ethical and clinical concerns, as individuals labeled as CHR may never develop psychosis yet still face stigmatization due to their risk status. Although research on the prodromal phase remains limited, emerging evidence suggests that early intervention during this stage can significantly reduce the likelihood of transition to active psychosis.[8]

1.3 Environmental Risk Factors

Environmental risk factors play a significant role in the development of schizophrenia, often interacting with underlying genetic predispositions. Key environmental contributors include prenatal complications, urban living conditions, and socioeconomic adversity. Prenatal exposure to maternal infections—particularly viral infections such as influenza, rubella, and toxoplasmosis—has been linked to an increased risk of schizophrenia in offspring. Furthermore, birth complications, including hypoxia (oxygen deprivation) and elevated maternal stress, may disrupt neurodevelopment and increase susceptibility to the disorder. Growing up in urban environments is also associated with a heightened risk of schizophrenia compared to rural areas. Contributing factors may include social isolation, environmental stress, pollution, and limited community cohesion, all of which are more prevalent in densely populated settings.[8]

Additionally, socioeconomic disadvantage—characterized by poverty, low educational attainment, unemployment, and social marginalization—has consistently been linked to increased schizophrenia risk. Other relevant factors include exposure to chronic stress, inadequate access to healthcare, and systemic social inequalities, all of which may exacerbate vulnerability to psychosis.[8]

1.4 Genetic Risk Factors

Schizophrenia is highly hereditary, as several genetic risk factors have been implicated. Individually unique genomic variations, otherwise known as copy number variations, have been linked to an increased risk of schizophrenia. These variations can arise through genomic mechanisms such as deletions and duplications of chromosomal segments. Additionally, Single Nucleotide Polymorphisms (SNPs) are genetic variations that can also lead to mutations that are associated with a higher risk of schizophrenia. Among these, variations in the Neuregulin 1 (NRG1) gene have garnered attention due to the gene's role in neural development, synaptic plasticity, and signaling pathways related to schizophrenia. Moreover, genes encoding proteins involved in dopaminergic neurotransmission have been extensively studied, supporting the dopamine hypothesis of schizophrenia. This theory

posits that dysregulation of dopamine pathways contributes to the positive symptoms of the disorder, such as hallucinations and delusions.[8]

1.4.1 Dopamine Hypothesis

The dopamine hypothesis is a long-standing theory suggesting that dysregulated dopamine activity contributes significantly to the pathophysiology of schizophrenia. Research has particularly implicated dopamine D2 receptors in the subcortical and limbic regions of the brain, where hyperactivity is thought to underlie positive symptoms such as hallucinations and delusions. Additionally, dopamine D1 receptors have been associated not only with positive symptoms but also with negative and cognitive manifestations of the disorder.[8]

The origins of the dopamine hypothesis stem from pharmacological evidence: antipsychotic medications such as haloperidol and clozapine reduce dopamine activity—especially by antagonizing D2 receptors—leading to symptom relief. Conversely, substances that elevate dopamine levels, such as amphetamines and cocaine, can induce psychotic-like behaviors in otherwise healthy individuals, further supporting the link between dopamine dysregulation and psychosis.[8]

Despite its foundational role, the dopamine hypothesis does not fully account for the wide spectrum of symptoms observed in schizophrenia. Current understanding acknowledges that the disorder likely results from complex interactions between genetic and environmental factors, potentially affecting early brain development and leading to broader neurochemical and structural abnormalities beyond dopamine alone.[8]

2. Background on Epigenetics

Epigenetics is the study of heritable changes in gene expression that occur without alterations to a DNA sequence itself. These changes are mediated by chemical modifications to DNA or histone proteins, as well as through non-coding RNA molecules. Epigenetic mechanisms play a crucial role in regulating gene activity in response to environmental cues, developmental stages, and cellular differentiation. They contribute to diverse processes that function throughout an organism's lifetime. Epigenetics provides insights

into how external factors influence genetic activity, offering profound implications for understanding disease susceptibility, evolution, and even personalized medicine. By unraveling the complexity of epigenetic marks, scientists are gaining new perspectives on human biology and the intricate ways in which our experiences leave lasting imprints on our genetic code.[9]

Epigenetics overall is a relatively new concept that is being put more into practice each year. The term "epigenetics" was created in the human biology setting by the embryologist Conrad Waddington in 1942. The biggest advancements in epigenetics and the understanding of them have occurred in the 21st century. This includes but is not limited to, a better understanding of DNA methylation, further development of CRISPR/Cas9 skills, more knowledge of histone modifications, and the expansion of knowledge of epigenetics with disease treatment.[9]

2.1 Epigenetic Mechanisms

Epigenetic mechanisms refer to reversible modifications that regulate gene expression without altering the underlying DNA sequence. These mechanisms include DNA methylation, histone modifications, and the regulation of gene activity by non-coding RNAs. Epigenetic modifications play crucial roles in various biological processes, including development, where they regulate gene expression during cell differentiation; differentiation, by influencing how stem cells mature into specific cell types; and disease, as seen in conditions like cancer, where abnormal DNA methylation patterns can lead to the silencing of tumor suppressor genes. These modifications can also affect brain function and contribute to neurodevelopmental disorders such as schizophrenia. Dysregulation of epigenetic mechanisms has been implicated in numerous diseases, including cancer, neurodevelopmental disorders, and autoimmune diseases.[9]

2.2 DNA Methylation

DNA methylation involves the enzymatic addition of methyl groups ($-CH_3$) to the cytosine residues of DNA, typically at CpG islands, which are regions rich in cytosine and guanine nucleotides. This epigenetic mark generally acts to suppress gene transcription by reducing the accessibility of DNA to transcription factors and other regulatory proteins. When

methylation occurs in promoter regions of genes, it often leads to transcriptional silencing, effectively turning the gene "off." Aberrant DNA methylation patterns—either hypermethylation or hypomethylation—are implicated in a wide range of diseases, including schizophrenia, where they may alter the expression of genes critical for brain development and function.[9]

2.1.1 Histone Modification

Histone modifications are chemical changes to the histone proteins around which DNA is wrapped to form chromatin. These modifications affect how tightly or loosely DNA is packaged and thereby influence gene accessibility and expression. Acetylation causes the chromatin to relax by neutralizing the positive charge on histone proteins, which lessens their attraction to negatively charged DNA and, therefore can assist with gene activation. Phosphorylation acts in a similar capacity to altering the histone charges, but instead, it can make it either relaxed or compact. Methylation is most commonly used to promote gene silencing by enhancing the interaction between the DNA and histones. Ubiquitination can play a dual role and could both loosen or compact the chromatin. Histones are proteins around which DNA is wrapped to form chromatin. They play a fundamental role in packaging and organizing DNA into a compact and orderly structure which is essential for the regulation of gene expression, among other processes.[9]

Additionally, non-coding RNAs—including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs)—contribute to epigenetic regulation by interacting with chromatin remodeling complexes and transcription factors. These RNA species can modulate gene expression post-transcriptionally or by guiding epigenetic modifiers to specific genomic loci, further increasing the complexity of epigenetic regulation in health and disease.[9]

2.1.2 Chromatin

Chromatin is the complex of DNA and proteins found within the nucleus of cells helping to organize and compact DNA within the nucleus into a manageable structure. Specifically, chromatins condense into visible chromosomes during cell division. It is important to note that its structure

is highly dynamic and can be altered by various epigenetic mechanisms such as DNA methylation, histone modifications, and non-coding RNA regulation. These epigenetic modifications regulate gene expression by controlling the accessibility of DNA to the transcriptional machinery. Essentially, chromatin structure and its modifications are central to the field of epigenetics, playing critical roles in the regulation of gene expression, cellular differentiation, development, and disease.[9]

2.2 Prior utilization of epigenetics in medical research

Although there has been slow progress in the implementation of epigenetic pharmaceuticals due to their low specificity, there are several medicinal drugs currently on the market for clinical use focused on modulating the epigenome. Controlling gene expression pre-transcriptionally is desirable in treating a variety of diseases. Epigenetic drugs targeting tumor and cancer growth have been approved by the FDA for oncological use.[9]

Histone deacetylase (HDAC) inhibitors and DNA methyltransferase (DNMT) inhibitors have also been suggested as epigenetic drugs that may be relevant in combating schizophrenia. Histone deacetylases are enzymes that remove acetyl groups on histones. This allows chromatin to wrap more tightly around histone proteins and thus serve as an obstacle to restrict transcription, eventually permitting the chromatin structure to be more relaxed and accessible for transcription factors. Therefore, histone deacetylases can help restore the normal expression of genes which can assist in alleviating symptoms such as cognitive impairments and memory deficits which are common symptoms of schizophrenia. DNMT contributes to the abnormal methylation of regions of DNA. Additional second and third-generation epigenetic drugs have explored additional enzyme inhibitors, however, ensuring low toxicity and high specificity has thus far proved to be a major hurdle. The use of DNMT inhibitors in schizophrenia treatment would assist in reversing abnormal DNA methylation patterns that may have contributed to the onset of schizophrenia.[9]

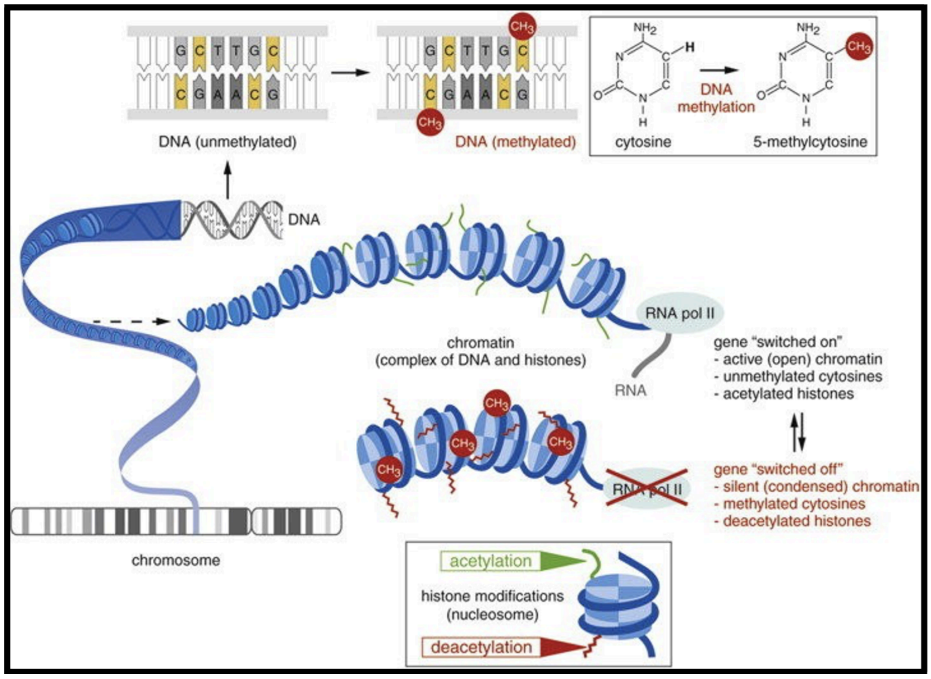

Figure 1: Chromatin modifications mediated by methylation and acetylation. *This figure illustrates the sequence of mechanisms that cause methylation–the addition of a methyl group on the DNA. It also shows the different effects of methylation in activating or inhibiting a gene's expression.*

3. Previous exclusion of Epigenetics in Schizophrenia research

Although schizophrenia is a disease with a known high heritability, and thus offers strong promise for early prevention through epigenetic treatment, there has been little to no high-quality research examining the potential for the use of drugs such as HDAC or DNMT inhibitors in responding to early psychotic symptoms. While the broader medical field has embraced the principle that prevention is the most effective form of treatment, and epigenetics has been extensively applied in oncology and other areas for identifying trauma-related and disease-specific biomarkers, the field of schizophrenia research has largely overlooked the potential of epigenetic approaches. This neglect may stem, in part, from the complex and multifactorial etiology of schizophrenia, which continues to resist simple genetic or biochemical explanations.[9]

Nevertheless, numerous well-characterized environmental and genetic risk factors—including prenatal infection, early-life stress, and gene variants—could serve as promising starting points for epigenetic investigation. Given that epigenetic modifications are reversible, unlike permanent gene-editing interventions, they offer a more flexible and potentially safer therapeutic avenue. This reversibility enables dynamic modulation of gene expression in response to treatment, positioning epigenetics as a compelling but underutilized frontier in schizophrenia research.[9]

4. Current Models of Interventional Treatment

The current treatment models for schizophrenia continue to rely predominantly on reactive interventions, initiated after the emergence of clinical symptoms, rather than on preemptive or preventive strategies.

4.1 Psychological Intervention

Psychological interventions, particularly psychosocial treatments, play an essential role in the comprehensive management of schizophrenia. Psychosocial treatment refers to a broad category of therapeutic approaches that involve not only the patient but also family members, caregivers, and support networks. These interventions may include individual or group therapy, family counseling, peer support groups, and community-based rehabilitation programs.[10]

Psychoeducation helps patients and their loved ones understand the condition and available treatment options. Additionally, psychosocial rehabilitation teaches patients skills to manage daily activities.[10] Although therapy is often incorporated into treatment plans after a formal diagnosis, emerging evidence supports its early integration. Cognitive Behavioral Therapy (CBT), in particular, has demonstrated effectiveness in reducing symptom severity, improving medication adherence, and enhancing overall psychosocial functioning. When combined with pharmacological treatment, CBT can contribute to more favorable long-term outcomes for individuals living with schizophrenia.[10]

4.2 Pharmacological Intervention

Pharmacological treatment for schizophrenia has been largely guided by the dopamine hypothesis, which attributes positive symptoms—such as hallucinations and delusions—to dopaminergic hyperactivity, particularly in the mesolimbic pathway. This model led to the development and widespread use of first-generation (typical) antipsychotics, such as chlorpromazine, which alleviate positive symptoms by blocking dopamine D2 receptors.[11, 12] However, this narrow pharmacological focus has several limitations. While effective for positive symptoms, D2 antagonists provide limited benefit for negative symptoms (e.g., lack of motivation, social withdrawal) and cognitive deficits, which often appear earlier and more persistently impair daily functioning. Moreover, excessive D2 receptor blockade is associated with significant side effects, including extrapyramidal symptoms and tardive dyskinesia, which may hinder long-term adherence. Current pharmacological strategies, therefore, risk overlooking core domains of the disorder that are critical to long-term recovery, highlighting the need for more holistic and targeted treatments—potentially including non-dopaminergic and epigenetic approaches.[12]

4.3 Limitations and Complications

Current schizophrenia treatment models often overemphasize the dopamine hypothesis, primarily targeting positive symptoms while overlooking the full spectrum of the disorder. Additionally, treatment typically begins after the onset of schizophrenia, despite evidence that early intervention during the prodromal phase may significantly reduce symptom severity or prevent full disease progression. Unfortunately, the prodromal stage remains under-researched and underutilized in preventative treatment approaches.

Psychological interventions, though beneficial, are commonly introduced only after initial symptom onset. Yet research indicates that earlier implementation may yield better outcomes. These interventions are often combined with pharmacological treatment, but their effectiveness depends heavily on patient engagement. A major barrier to treatment is anosognosia—a condition in which individuals are unaware of their own illness, often due to delusions, hallucinations, or disorganized thinking.

Anosognosia complicates medication adherence and therapy participation, as patients may not recognize their need for treatment. Furthermore, individuals with schizophrenia often score low on conscientiousness, a personality trait linked to routine and self-discipline. As a result, they may struggle to follow structured treatment regimens, such as attending therapy or taking medication consistently. When treatment is delayed until later stages of illness, these challenges can become even more pronounced.

There is also the risk of the affected individual developing anosognosia if treatment isn't sought out before the full onset of symptoms. Anosognosia affects individuals who do not believe they have a disability and therefore do not seek out treatment. They often actively avoid any assistance offered. Therefore, the current models of interventional treatment will not be effective due to needing participation from the individual. Potentially, their symptoms could have been first eased by preventative treatment, so they lessen their chances of developing anosognosia by the time of the onset of symptoms.[13]

Cultural and socioeconomic barriers also contribute to delayed or avoided treatment. In some contexts, individuals may fear discrimination, stigmatization, or the loss of legal and social rights following a psychiatric diagnosis. In many countries, limited access to affordable mental health care—including psychiatric evaluations and follow-up services—remains a significant obstacle, particularly in low-income or rural areas.[13]

Table

Consequences of anosognosia in schizophrenia

Refusing hospitalization for psychosis, which is associated with neurotoxicity, leading to a longer duration of untreated psychosis and significant gray and white matter loss (via neuroinflammation and oxidative stress)
Poor treatment adherence, leading to recurrent psychotic relapses, with progressive neurodegeneration and brain atrophy
Treatment resistance due to frequent psychotic relapse and structural brain changes after each psychotic episode
Increased utilization of health care, especially emergency care
High risk of suicide, especially early after onset
Increased risk of aggressive behavior and violence towards others
Functional disability (school or work)
Incarceration due to psychotic behavior during relapses
Homelessness
Early mortality due to neglect of physical health, and lack of response to physical cues of illness

Figure 2: The Consequences of Anosognosia in Schizophrenic Individuals[13]

5. Epigenetic Regulation in Preventative Treatment

5.1 Psychological Potential

Therapy and broad psychological intervention are already an established part of schizophrenic intervention plans; however, the connection between psychological stress and its epigenetic impact on an individual's risk for developing schizophrenia has not been greatly explored as a means of early prevention. Awareness about the transgenerational effects of prenatal maternal stress and the promotion of cognitive behavioral therapy in at-risk individuals are promising as early responses to pre-psychosis.[13]

5.1.1 Prenatal Sensitivity to Stress

Prenatal maternal stress (PNMS) is defined by a pregnant woman experiencing stress during her pregnancy whether it is physical or psychological. The fetus can sense stress stimuli through elevated levels of maternal stress hormones, such as cortisol, which can cross the placenta. This exposure may trigger physiological adaptations, potentially altering gene expression. During development, the fetus takes cues from its environment to optimize its growth and function, but excessive stress exposure can lead to long-term changes in brain structure and function. This can alter the expression of the fetus' genes because, during development, the fetus takes cues from its environment on how best to develop.[14]

It has been shown that PNMS in combination with other factors such as genetic disposition and childhood trauma increases the risk of schizophrenia. It has been shown that individually, PNMS does not have a statistically significant effect on the fetus in developing schizophrenia. However, it is important to acknowledge PNMS' role in combination with other factors that influence schizophrenia to help identify high-risk individuals and be able to create an early intervention plan. PNMS has also been shown to affect sleep, diet, and inflammation which could also contribute to schizophrenia development. Identifying PNMS' role in affecting other factors that could contribute to schizophrenia, is crucial in order for more research to be conducted on PNMS' indirect effect on the development of schizophrenia.[14]

5.1.2 Individual Therapy and Psychoeducation

Cognitive Behavioral Therapy (CBT) is a widely practiced, evidence-based psychotherapy that targets maladaptive thoughts, emotions, and behaviors to improve overall mental health. When applied during the prodromal phase of schizophrenia, CBT has been shown to reduce the risk of transition to active psychosis, making it a promising early intervention strategy[15]. Additionally, enrolling at-risk individuals in psychoeducational programs may help prevent behaviors linked to schizophrenia through epigenetic pathways.[15]

One notable comorbidity of schizophrenia is substance abuse, particularly the high prevalence of tobacco use among individuals with the disorder. A leading theory suggests that tobacco may serve a self-medicating function, offering short-term cognitive benefits for patients by interacting with epigenetic mechanisms. Animal studies have demonstrated that nicotine exposure reduces levels of DNA methyltransferase 1 (DNMT1) in telencephalic GABAergic neurons in the frontal cortex—a brain region critical to cognition. DNMT1 is an enzyme responsible for methylating CpG islands, which suppresses gene transcription and plays a vital role in maintaining epigenomic stability. Notably, elevated DNMT1 levels have been observed in the GABAergic neurons of patients with schizophrenia[16]. This suggests that nicotine's ability to lower DNMT1 expression may temporarily improve cognitive function, potentially explaining the high rates of tobacco use in this population.[16]

However, despite these cognitive effects, the long-term consequences of tobacco use remain profoundly harmful. Integrating psychoeducation into early intervention programs could help at-risk individuals understand the biological basis of their susceptibility to tobacco use and inform more tailored, health-conscious treatment plans. This approach may enhance both the prevention and management of schizophrenia by addressing underlying epigenetic vulnerabilities.[16]

5.2 Pharmacological Potential

As the majority of schizophrenia treatments have focused on treating the dopaminergic pathway and the subsequent positive symptoms, the

pharmacological potential of epigenetically adjusting abnormal levels of other neurotransmitter pathways has been overlooked. In the prodrome, where negative and cognitive symptoms take precedence over positive symptoms, epigenetically regulating other neurotransmitter pathways that are imbalanced through pharmaceuticals could prove to be a powerful preventative measure against full schizophrenic onset.[17]

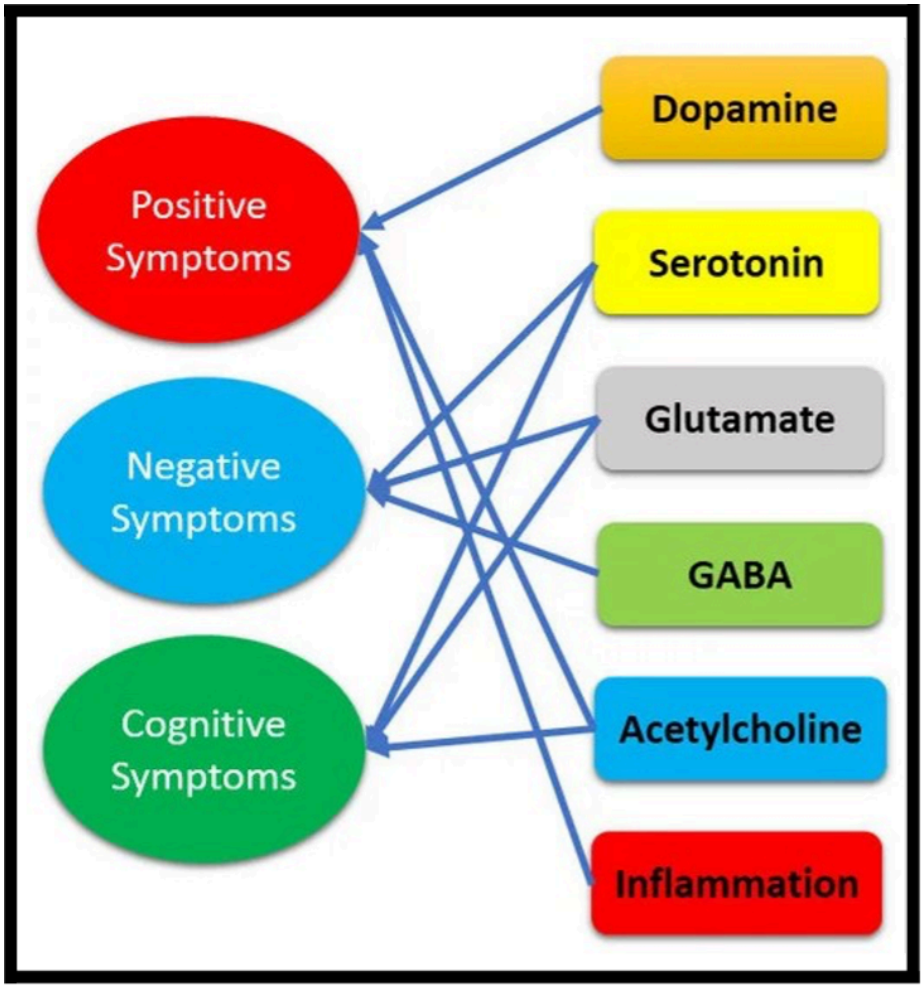

Figure 3: A chart depicting the contributors to each kind of schizophrenic symptom category. *Figure 3 shows the relevant neurotransmitters and their connections to each of the three symptom categories of Schizophrenia. Certain neurotransmitters play little to no role in contributing to certain symptoms, so this serves as a means of narrowing what is worth researching for treatments for specific symptoms.*

5.2.1 DNA Methylation Focused Pharmacologic Treatment

Multiple post-mortem studies of patients with schizophrenia have identified hypermethylation in the promoter regions of genes in GABAergic neurons, leading to reduced GABA neurotransmission—a key inhibitory process in the brain.[17] This epigenetic suppression results in the downregulation of mRNA for glutamic acid decarboxylase 67 (GAD67) and reelin (RELN), both of which are crucial for normal synaptic function. GAD67, encoded by the GAD1 gene, catalyzes the conversion of glutamate to GABA, and its reduced expression in the prefrontal and temporal cortices has been associated with cognitive impairments, particularly deficits in working memory and executive function, seen in individuals during the prodromal phase of schizophrenia.[18]

Another promising molecular target is the neural cell adhesion molecule (NCAM), a glycoprotein involved in axon growth, synaptic plasticity, and neuronal migration. NCAM is found to be overexpressed in the prefrontal cortex and hippocampus of individuals with schizophrenia. In animal studies, the presence of anti-NCAM1 autoantibodies has induced schizophrenia-like behaviors, suggesting that such antibodies could serve as a biomarker for the disease.[18]

The elevated levels of DNA methyltransferase 1 (DNMT1) found in patients with schizophrenia can potentially be normalized through the use of DNMT inhibitors or DNA demethylation inducers. DNMT inhibitors prevent the addition of methyl groups to DNA, while demethylating agents remove existing methyl marks. Both strategies may restore GAD67 and RELN expression, thereby enhancing GABAergic signaling and potentially ameliorating cognitive and synaptic deficits associated with the disorder. As epigenetic regulators, these agents offer a promising route to reverse transcriptional repression of key genes implicated in schizophrenia.[18]

5.2.2 Histone Modification-Focused Pharmacologic Treatment

Previous epigenetic research has found that schizophrenic-like symptoms can be replicated by administering mitotoxin (a cytotoxic molecule that causes cell death by interfering with protein or DNA synthesis) on day 17 of the embryonic prenatal stage. The mitotoxin administration had several

effects on various epigenetic mechanisms, including decreased methylation in certain promoter zones of cannabinoid receptor 1.[19-23]

Using MAM-E17 has replicated schizophrenic symptoms and has also been used as a method to examine the impact on histones. Tri-methylated histone H3 at lysine (K) (H3K4me3) facilitates gene transcription by opening chromatin. The opening of chromatin, allows transcriptional mechanisms such as RNA polymerase and transcription factors to have better access to the DNA, which means the genes are more likely to be activated. MAM-E17 experimentation has found lower levels of H3K4me3 near GAD1 promoters, thereby hindering the production of GABA[23]. Adjusting the expression of the SETD1A gene may be an epigenetic point of interest, as this gene regulates the downstream levels of H3K4me3.[23]

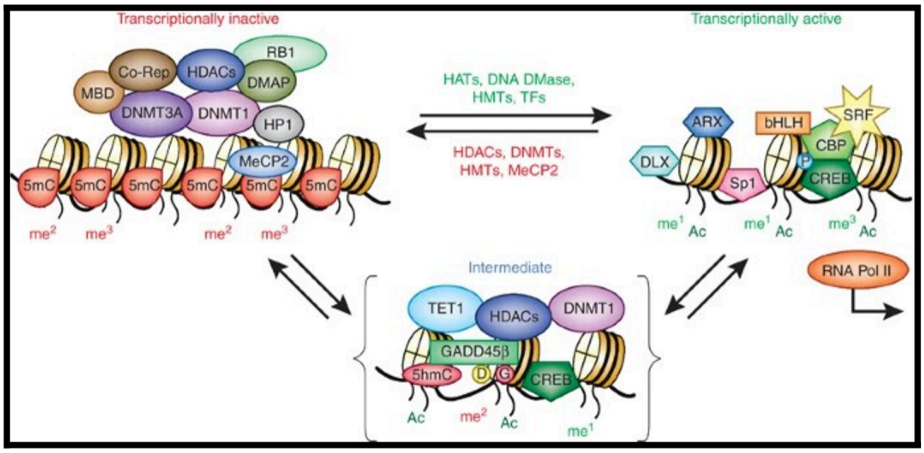

Figure 4: A chart detailing the inhibitory or excitatory effects of various pharmaceuticals targeting histones. *This figure shows the way in which epigenetic therapeutics target transcription, when DNA gets copied into RNA. When transcription is inhibited and inactive, proteins are not produced, and the gene is not expressed.*

5.3 Epigenetic biomarkers

In identifying individuals at risk for schizophrenia, an accurate and reliable screening method is necessary. H3K4me3 deficits near GAD1 promoters have been noted in people with schizophrenia[23]. Brain-derived neurotrophic

factor (BDNF) levels were found to be frequently elevated along with C-reactive protein (CRP) elevation[24]. These may both contribute to lowered cognitive function or dysregulation in patients suffering from schizophrenia. Unfortunately, there are very few identified reliable biomarkers for the prodromal period of schizophrenia. This may be influenced by the difficulty of enrolling prodromal individuals into invasive trials to reliably determine prodromal biomarkers. However, biomarkers already associated with schizophrenia are suggested to be prodromal biomarkers as well. A deletion of a piece of chromosome 22 (22q11.2), noted in about 1% of all individuals with schizophrenia, is also theorized to be a genetic risk factor and subsequent biomarker of schizophrenia.[25] Certain biomarkers also suggest the role of prenatal stress in the potential for developing schizophrenia. DNMT1 and TET1 were found to be higher in prenatally stressed mice and are promising early biomarkers as well.[26]

5.4 Methods for Screening for Epigenetic abnormalities and markers

Since biomarkers are relatively unreliable for early detection of prodromal schizophrenia on their own, additional screening measures should be used. Individuals with a reported familial history of schizophrenia may be recommended to partake in regular annual screenings to catch early identifiers due to the high heritability of schizophrenia. The medical field already often suggests annual check-ups and screenings such as pap smears during certain years of life. This is less common regarding mental health and neurodevelopmental disorder prevention, likely contributed to by significant historical stigma regarding psychiatric disorders and mental illness. Recently, similar propositions for recommended mental health check-ups have been suggested by psychologists and psychiatrists alike, although little progress has been made as of yet.[27]

There are a variety of symptom screening tests to identify early prodromal symptoms. The Structured Interview for the Prodromal Syndrome (SIPS), paired with the Scale of Prodromal Symptoms (SOPS), has been reliable and used in many clinical trials to determine individuals at high risk of developing psychosis. In SIPS, a clinician performs a lengthy interview with the patient examining their psychological, social, and health history. Using

SOPS, the patient's responses are ranked on a four-item scale based on positive, negative, disorganized, or general symptoms. Individuals may be classified as being already psychotic, at high risk for psychosis, or not at risk for psychosis.[27]

The third syndrome diagnosis is the least common, but highly relevant to those with schizophrenia, being the Genetic Risk and Deterioration Prodromal Syndrome (GRDS)[27]. Individuals with a general decline or deterioration in their well-being who have a first-degree relative with a history of a psychotic disorder or who may have a schizotypal personality disorder may be diagnosed with GRDS.[27]

The Positive and Negative Syndrome Scale (PANSS) also utilizes a clinician-based interview and has been used since the 1980s to measure the severity of symptoms in affected individuals. It has use in screening for early psychosis as well, although its interview questions are less focused on identifying prodromal individuals similar to the Basel Screening Instrument for Psychosis (BSIP).[27]

The Comprehensive Assessment of the At-Risk Mental State (CAARMS), is often used alongside SIPS/SOPS to determine prodromal individuals for early psychosis. It is reliable in tracking the development of psychosis and the onset of the FEP. CAARMS includes many subscales that measure the well-being of various aspects of the individual's life and includes many interview questions across seven domains of interest in order to appropriately gauge the individual's risk. Questions may explore the individual's psychopathology, positive and negative symptoms, changes in their cognition, emotions, behavior, and physiology. CAARMS uses the Social and Occupational Functioning Assessment Scale (SOFAS), which rates individuals similarly to SOPS and determines if they meet the criteria for full onset psychosis, BIPS, or APS.[27]

A major obstacle with prodromal screening is that they often require highly trained clinicians who can offer appropriate interviews. The interviews themselves can also be quite lengthy and inaccessible to individuals who have significant life obligations.[27]

6. Discussion

Developing pharmaceuticals that target the epigenome has historically proven to be a challenging endeavor, which has discouraged widespread research into their therapeutic potential. Compounding this difficulty are ethical concerns related to privacy and genetic data, which have further hindered funding and institutional support for epigenetics research. As a result, the application of epigenetic therapeutics in schizophrenia treatment remains limited, despite substantial evidence supporting its promise. Currently available epigenetic drugs often suffer from issues such as low target specificity, off-target effects, and high toxicity, reducing their viability in clinical settings. Furthermore, many research institutions prioritize areas with higher academic prestige or more secure funding, creating a significant opportunity cost for pursuing epigenetics-based research. These factors have collectively slowed progress in exploring how epigenetic interventions could be used to prevent schizophrenia and other neurodevelopmental disorders.

Nonetheless, recent advances in developmental psychology and genetics have contributed to the reframing of the nature vs. nurture debate, now widely accepted as an interactionist model. The consensus among psychologists is that both genetic predispositions and environmental exposures influence developmental outcomes, including disease susceptibility. This evolving perspective has opened the door for greater exploration of epigenetics in medicine, as it accounts for how environmental factors can modulate gene expression without altering the DNA sequence. In the case of schizophrenia, while heritability remains high, growing evidence indicates a significant interplay between epigenetic modifications and environmental influences in shaping the onset and progression of the disorder.

As discussed in Section 4.2, pharmacological intervention — particularly the use of antipsychotic medications—remains the most common treatment model for schizophrenia. These medications have proven effective in reducing positive symptoms such as hallucinations, delusions, and disorganized thinking by modulating dopaminergic activity [21]. However, research also shows that pharmacological treatments are most effective when combined with psychological therapies, such as Cognitive Behavioral

Therapy (CBT), which equip patients with coping strategies and cognitive restructuring tools.

Despite the therapeutic utility of antipsychotics, there is a growing need to shift the focus toward prevention. Early-stage, non-pharmacological interventions may help delay symptom onset, reduce severity, and lessen reliance on medication. Preventative treatment is particularly important for individuals who cannot tolerate antipsychotic medications due to severe side effects or treatment-resistant schizophrenia[22]. Given the unpredictability of medication efficacy and tolerability, alternative or complementary preventative strategies are critical to improving outcomes.

Another vital consideration is the social stigma historically associated with schizophrenia and other psychotic disorders. Being labeled as "at risk" for psychosis can significantly impact a person's self-perception, social standing, and mental health, even if symptoms never manifest. Stigma may lead to ostracization, bullying, or discrimination, particularly if peers or family members are unfamiliar with the disorder. These social pressures may contribute to the development of comorbid conditions, such as depression, anxiety, or panic disorders.

Therefore, any preventative framework for schizophrenia must be implemented with cultural sensitivity and clinical precision. Accurate screening tools are essential to avoid false positives and mislabeling, which may do more harm than good. Furthermore, public education is a key component of reducing stigma. Increasing awareness and understanding of mental disorders among the general population can foster a more supportive and inclusive environment for those identified as at risk. Building such a community is vital—not only for the effectiveness of treatment but also for maintaining morale, social integration, and overall mental well-being.

7. Conclusion

The field of schizophrenia research has historically underemphasized prevention, despite mounting evidence supporting the efficacy of standardized preventative measures, including psychoeducation, therapy, early detection, and epigenetic interventions. As a result, many individuals

continue to suffer from lifelong, severe symptoms that might have been mitigated—or even prevented—through early response strategies. Stigma surrounding schizophrenia further delays diagnosis and treatment, exacerbating the burden on affected individuals. Emerging research suggests that epigenetics may offer a powerful avenue for early intervention by enabling reversible modifications to gene expression. These interventions have the potential to reduce symptom severity or prevent the onset of psychosis altogether. To fully realize this potential, greater investment is needed from pharmaceutical and biotechnology companies, as well as from clinical psychologists, to explore the interplay between epigenetic regulation and schizophrenia pathophysiology.

Though still a developing field, epigenetics presents transformative possibilities not only for schizophrenia but also for a broad spectrum of conditions, including neurological disorders, autoimmune diseases, metabolic syndromes, and cardiovascular conditions. Continued exploration and application of epigenetic science stand to advance both preventive medicine and precision therapeutics, reshaping the future of healthcare.

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