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Schizophrenia: Epidemiology, Causes, Neurobiology, Pathophysiology, and Treatment

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Abstract
Schizophrenia is a severe mental illness that has devastating consequences for those who suffer from the disorder. The epidemiology of schizophrenia indicates that it occurs relatively often, in many different contexts, and in conjunction with other disorders, decreasing quality of life and causing premature death. There has been an enormous amount of research into the causes of schizophrenia and there is now have a much better understanding of the genetic, environmental, and psychological factors that contribute to the disease. While there are numerous ways to understand and conceptualize schizophrenia, a unified picture of the neurobiology, changes in brain structure, cognitive and social-cognitive impairments related to the disorder has yet to emerge. Convulsive therapies and psychosurgery were used unsuccessfully, indiscriminately and without scientific validation in the past to treat schizophrenia. Medical advances including advanced imaging technology have now provided the ability to perform specifically focused neuromodulation and psychosurgery in severe and treatment resistant cases of schizophrenia. While still at a preliminary stage, these approaches have the potential to yield effective treatments in the future. For the last 70 years antipsychotic medication has become the prevailing treatment for schizophrenia. However, many people suffering from the disorder have trouble with side-effects and adhering to a regimen of antipsychotic medication. Newer pharmacological agents are being developed and include not only novel antipsychotic drugs, but anti-inflammatory and immunomodulating agents as well. These new agents, used either alone or in combination, have the potential to improve outcomes for people suffering from schizophrenia. Nevertheless, conclusively better pharmacotherapies will likely not arise until there is better understanding of the pathophysiology underlying schizophrenia. After the development of antipsychotic medication, psychotherapeutic methods for treating schizophrenia fell out of favor, but there is currently some reversal of this trend. The use of newer psychotherapies and modified forms of older therapeutic treatments are not only targeting the symptoms of schizophrenia but are also now focusing on recovery from the disorder. These newer approaches as well as efforts at preventing schizophrenia show promise in reducing the suffering caused by this disease.

Keywords: Schizophrenia, Autoimmunity, Brain Structure, Antipsychotic Medication, Neuromodulation, Psychotherapy

1. Introduction

Schizophrenia is the term for a mental disorder in which thought and perception are severely impaired. People suffering from schizophrenia have delusional beliefs and, in many instances, these are accompanied by auditory or visual hallucinations. People with schizophrenia display disorganized thinking that can manifest as bizarre personality and behavioral changes that cause impairment in social functioning. The person suffering from schizophrenia demonstrates a marked loss of contact with reality.

The fifth edition of The Diagnostic and Statistical Manual of Mental Disorders (DSM V) now understands all psychoses as variants of schizophrenia (American Psychiatric Association, 2013). This schizophrenia spectrum includes schizophrenia, other psychotic disorders, as well as schizotypal disorder (which is generally diagnosed as a personality disorder). The DSM V lists the following schizophrenia spectrum disorders: *schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, substance/medication induced psychotic disorder, psychotic disorder due to another medical condition, unspecified schizophrenia and other psychotic disorder* (pp. 87-160). When we examine these schizophrenia spectrum disorders, it becomes obvious that there are many similarities among the disorders and that they differ only in duration or emphasis on a particular symptom. For instance, schizophrenia, schizophreniform disorder, and brief psychotic disorder differ in terms of duration, while schizophrenia, delusional disorder, and schizoaffective disorder differ in symptomatic content[1]. Psychotic disorder due to a general medical condition and substance-induced psychotic disorder are both related to psychoses that result from chemical or structural changes in the body. What is clear from all these descriptions is that schizophrenia encompasses all the psychotic characteristics of these disease entities. Another way of saying this is that all these disorders are easily understood as variations of schizophrenia. For that reason, our discussion will focus on schizophrenia.

Schizophrenia presents with symptoms that can be positive, negative, or mixed. Positive symptoms of schizophrenia include overt delusions, auditory, visual, and tactile hallucinations, thought disorder, and behavior that is bizarre when compared to normal behavior in the culture where it occurs. Negative schizophrenic symptoms include a flat affect, alogia, avolition, anhedonia, and impairment of attention. Cognition may also be impaired in those who have the disease with consequences for social functioning (Rossello et al., 2013). Mixed schizophrenic symptoms that include both positive and negative symptoms may also occur (Dion & Dellario, 1988).

2. Epidemiology of Schizophrenia

Schizophrenia typically has an onset in adolescence or young adulthood and most estimates are that approximately 1% of the population is affected (Castle & Morgan, 2008). A review of prevalence data from a large number of geographically diverse studies indicates lifetime prevalence ranging from around .2% to almost 1.5% (Simeone et al., 2015). Men are significantly more likely than women have the disorder (Grignon & Trottier, 2005). While it has commonly been held that prevalence rates for Schizophrenia are fairly stable around the world (Nixon & Doody, 2005), some studies are now questioning this dogma, demonstrating that sex, age, ethnicity, and geography are related to its incidence (McGrath et al., 2011; McGrath, 2006). Other studies have shown increasing general rates of schizophrenia (Boydell et al., 2003; Bray et al., 2006) while others have not (Nixon & Doody, 2005; Suvisaari et al., 1999).

There is some debate about whether schizophrenia represents a single disease or many different syndromes. This idea is supported by some studies that have found that different biological markers are associated with how well patients respond to antipsychotic drugs (Garver et al., 2000). The presence of these different biological markers gives support to the idea that schizophrenia may in fact be multiple syndromes rather than a single disease entity. Ross (2014; 2006) argues against the prevailing view schizophrenia is primarily an inherited biological disorder to be treated solely with medication. He goes on to make the case for viewing the positive symptoms of schizophrenia as being more representative of dissociative identity disorder and proposes a dissociative subtype

[1] Some researchers question whether or not schizoaffective disorder is really a separate disorder and not either a variation of schizophrenia or mood disorder (Cheniaux et al., 2008; Marneros, 2007). In fact, scientists and clinicians continue to debate just what constitutes a psychosis (Castle & Morgan, 2008).

of schizophrenia. Kroll (2007) after reviewing many cross-cultural studies of psychoses concludes that there are so many shared risk factors for psychosis and affective disorders that he questions whether or not there should be a categorical distinction between disorders.

3. Co-Morbidity and Mortality

People who suffer from schizophrenia often suffer from other mental health issues such as anxiety disorders, depression, and substance abuse, as well as from physical problems related to cardiovascular, oral, respiratory and endocrine pathology (Laursen, 2019; Laursen et al., 2012). People with schizophrenia may have more risk of contracting COVID-19 (Fonseca et al., 2020; Kozloff et al., 2020). Some of the problems stem from unhealthy behavior patterns related to smoking, eating, and sexual behaviors, which are preventable (Arnaiz et al., 2011; Chwastiak & Tek, 2009; Findlay, 2015; Trudeau et al., 2018). As might be expected, the presence of co-morbid conditions is associated with worse symptoms, treatment outcomes, and social functioning (Pratt, 2012; Sim, Chan, et al., 2006; Sim, Chua, et al., 2006). People who suffer from schizophrenia often have social dysfunction. They are more likely to be unemployed, poor, and homeless. Unfortunately, this leads to decreased life expectancy with some estimates as much as 10-12 years less than people who do not suffer from schizophrenia (S. Brown et al., 2000). Other studies have shown that on average individuals with schizophrenia live about 36 years after diagnosis and that this number is decreasing (Capasso et al., 2008; Sukanta Saha et al., 2007).

After reviewing more than forty thousand studies Leucht et. al. (2007) concluded that individuals suffering from schizophrenia in developed nations have increased rates of HIV, hepatitis, osteoporosis, sensitivity to pain, sexual dysfunction, obstetric complications, cardiovascular diseases, obesity, diabetes, dental problems, and polydipsia when compared to the general population. Interestingly, people suffering from schizophrenia were found to have lower rates of rheumatoid arthritis and cancer. The authors conclude that many of these medical problems may be related to the treatment delivered by health services as well as the social stigma attached to the disease.

Infection with *Toxoplasma gondii* (T. gondii), which has been suspected of contributing to the development of schizophrenia (see below), has also been associated with increased mortality among schizophrenia sufferers (Dickerson et al., 2007). Long-term use of antipsychotic medication is also suspected of decreasing life expectancy in people suffering from schizophrenia (Fors et al., 2007; Healy, 2006; Joukamaa et al., 2006). Antipsychotic medications may increase mortality among individuals suffering from schizophrenia by contributing to obesity, hyperglycemia, diabetes mellitus, and dyslipidemia (Casey et al., 2004; Robinson, 2008). One study reported that people suffering from schizophrenia who use antipsychotic medication were five times more likely to suffer from a heart attack than healthy controls (Enger et al., 2004). Suicide is found more often in people suffering from schizophrenia with males having higher rates of mortality (Lester, 2007). This finding is seen across cultures and may explain the higher prevalence of schizophrenia among females in some areas (Ran et al., 2007).

4. Causes of Schizophrenia

It is still not known what causes schizophrenia and how it develops. Yet researchers are cautiously optimistic that we will soon have some answers regarding the etiology of this disease (Schwab & Wildenauer, 2008). While generally thought to be a disease of the brain, studies suggest that genetics, early environment, psychological, and social processes are important contributory factors to its development (K. Dean et al., 2003; Gilmore, 2010). Indeed, there is recent support for the older idea of psychogenic causes or contributions to the development of the disease. As Lublin and Erbehard (2008) put it:

> *"Basic research into the mechanisms behind the disorder suggest that the possibility of psychogenesis still appears to have some validity, although we may never entirely come to understand the relationships and possible interactions between the environmental and genetic risks…We know that, like many other disorders, there are susceptible individuals who appear to have inherited a number of genetic traits, each of which is also present in the general population, but which, together, render that individual vulnerable to schizophrenia. These include neurodevelopmental genes — but they are by no means the whole story…there is still much work to do on our understanding of the contribution of early environmental 'insults' such as prenatal infections, maternal malnutrition, substance abuse, and obstetric complications…"* (p. v)

Schizophrenia is thought to have a genetic component and having first degree relatives with the disorder greatly increases the risk of developing schizophrenia. Recent research indicates that mutations at genetic loci related to schizophrenia are heterogenous, with a relatively weak contribution on of any single mutation (Zhenxing et al., 2018).

Torrey et. al. (2012) report on a number of causative risk factors for schizophrenia. Having a mother with schizophrenia raises risk of the disorder about 9 times, while having a father or sibling with the disorder increases risk about 7 times. However, other risk factors abound. Being the offspring of an immigrant increases risk of schizophrenia 4.5 times while being an immigrant from or to certain countries increases the risk 2.7 times. T. gondii infection results in a 2.7 times greater risk. Being born or raised in an urban setting increases risk 2.2 – 2.8 times, while cannabis use, minor physical abnormalities, and having a father over 55 at time of birth results in around 2 times the risk. The authors found other risk factors to have minor impacts, increasing the risk of schizophrenia 1-1.7 times. These factors include traumatic brain injury, being sexual abused as a child, complications during birth, having a father 45 or older at birth, season of birth, having specific genetic variations, and maternal exposure to the flu. Some of these factors are discussed below.

5. Childhood Abuse, Trauma, and Schizophrenia

The association between childhood abuse and subsequent diagnosis of schizophrenia is complicated. There have been a number of studies that indicate a relationship between childhood abuse and schizophrenia. Read et. al. (2003) found that abuse as a child (sexual and physical) was significantly related to hallucinations, but not delusions, thought disorders, or negative symptoms among community mental health center clients. Child abuse and subsequent abuse as an adult, predicted hallucinations, delusions, and thought disorders.

Read et. al. (2005) in a systematic review of the literature found a strong causal association between child physical and sexual abuse, and schizophrenic symptoms, especially hallucinations. This review also supports the idea of a dosage effect with higher levels of abuse being associated with more severe psychotic symptoms. The authors conclude that many severe mental illnesses, including schizophrenia as well as post traumatic stress syndrome and other diagnoses related to dissociation (e.g. borderline personality disorder and dissociative disorders) can be understood as adaptive responses to early childhood trauma which are subsequently maladaptive in adults.

Janssen et. al. (2004) in a study of over 4000 subjects drawn from a general population found that people who had suffered abuse as a child were 7.3 times more likely to develop positive schizophrenic symptoms compared to those who had not been subjected to abuse as a child after adjustment for confounding. This study also demonstrated a dose-effect with those having experienced higher levels of abuse having more severe psychotic symptoms. Those subjects with the highest frequency of abuse as children were found to be 30 times more likely to have psychotic symptoms than those who were not abused.

While many studies show a strong association between childhood sexual and physical abuse and schizophrenia, other studies have found conflicting results. Spataro et. al. (2004) in a study of 1612 sexually abused children found significant rates of affective disorders, anxiety disorders, childhood mental disorders, and personality disorders, but not schizophrenia. It may be that the associations in many studies were related to schizophrenic symptoms but not the fully diagnosable disorder (Mullen, 2005).

Lysaker et. al. (2001, 2004, 2005) found that childhood sexual abuse victims who were later diagnosed with schizophrenia spectrum disorders reported higher levels of psychotic symptoms, as well as poorer psychosocial functioning and participation in vocational rehabilitation. The subjects who suffered from schizophrenia were also more likely to perform worse on tests of executive function and have higher levels of hallucinations and anxiety. A similar study by Gil et. al. (2009) found that adult patients diagnosed with schizophrenia (but not having an acute psychotic episode) had increased disability, functional impairment in overall behavior, social role performance, and global functioning (which was derived from a combination of the other measures). Higher emotional abuse was associated with impaired overall behavioral functioning and higher emotional neglect was

associated with a decrease in global functioning. Physical neglect was associated with the subjects' overall ability to function as adults. There was no association found between sexual and physical abuse and schizophrenia.

Schürhoff et. al. (2009) found a strong correlation between childhood trauma and positive schizotypal tendencies among unaffected first degree relatives of people suffering from schizophrenia. A correlation between childhood trauma and bi-polar tendencies was not found among the relatives of subjects with bi-polar disorder. Vogel et. al. (2011) compared non-psychotic subjects and adult subjects suffering from schizophrenia and found that childhood abuse was related to non-psychotic disorders while neglect was related to development of schizophrenia. It was thought that childhood abuse can cause different symptoms in adults with psychotic and non-psychotic disorders. Ashcroft et. al. (2012) in a study of patients suffering from schizophrenia found that those with persecutory delusions reported significantly more emotional abuse than those patients without these delusions. There was no difference in these two groups with regard to total trauma, physical abuse, physical neglect and sexual abuse. Leonhardt et. al. (2015) found that patients suffering from schizophrenia with increased awareness and concomitant increased distress were more likely to have experienced abuse as children. A study by Kelly et. al. (2016) found a positive relationship between men and women diagnosed with schizophrenic and schizoaffective disorders and childhood abuse. Women who were sexually abused as children were more likely to show significantly more psychotic and depressive symptoms compared to women without childhood trauma and men with and without childhood trauma. A study by Kim et al. (2018) examined the relationship between childhood trauma and delusions and hallucinations among 42 subjects diagnosed with schizophrenia. Delusions of reference, persecutory delusions, and delusions of being controlled were found to be related to childhood emotional abuse. Childhood abuse and neglect was not found to be related to hallucinations.

Rokita et. al. (2020) found that patients suffering from schizophrenia were significantly more likely to recall childhood trauma and scored lower on social-cognitive measures and measures of parental bonding. Physical neglect was the strongest predictor of impairment in the ability to recognize emotions in others. Good bonding with parents attenuated the impact of childhood trauma and impairment in emotional recognition.

Overall, the preponderance of the evidence is that there is a relationship between childhood abuse and schizophrenic symptoms. A dose-effect relationship has been demonstrated in many studies where an increase in child abuse leads to worse schizophrenic symptoms and negative effects of the disorder. Emotional abuse seems to show a relationship to schizophrenic symptoms in many studies, while the specific contributions of neglect and sexual abuse to the development of schizophrenia have been mixed. Likewise, the relationship between child abuse and the development of delusions and hallucinations is mixed with some studies reporting a positive association with these symptoms and others not. More research with large populations examining different types of specific types of child abuse and trauma with schizophrenia is in order. Given what is known, however, clinicians working with those suffering from schizophrenia would do well to consider the possibility and effects of child abuse among their clients.

6. Drug Abuse and Schizophrenia

While both schizophrenia and drug abuse typically have onset in adolescence or young adulthood the relationship between them is not clear. It may be that vulnerability to substance abuse disorders and schizophrenia involve a similar neurobiological substrate (Murray et al., 2003; Zullino et al., 2010). Some studies suggest that drug abuse may in fact be causally related to later development of schizophrenia. This is especially likely for dopaminergic substances such as amphetamines, cocaine, and cannabis (Tsapakis et al., 2003; Weiser et al., 2003). Other studies suggest that drug use among people suffering from schizophrenia may be related to emotional abuse and that they use drugs mainly for social reasons (Gearon et al., 2001). Genetically vulnerable individuals who have experienced high stress events, and who use drugs may be especially at risk for developing schizophrenia (P. Miller et al., 2001). Nevertheless, there is also evidence that substance abusers with schizophrenia do not suffer from increased neuropsychological impairments and exhibit fewer negative symptoms (Joyal et al., 2003).

Cannabis use has especially been linked to schizophrenia in a number of studies (Roser, 2019). Cannabis is thought to double the risk of developing schizophrenia in vulnerable people. Heavier dosage and early age of use are associated with increased risk (Ortiz-Medina et al., 2018). A large study of young adults aged 18-34 which looked

at risk factors for schizophrenia found that a diagnosis of schizophrenia was associated with a history of trauma, a family history of drug problems, bisexuality, use of cannabis, cigarettes and alcohol, as well as drug use before the age of 16. The majority of people who developed schizophrenia used both cannabis and cigarettes. The researchers concluded that there was little support for an association between cannabis use and the development of schizophrenia after adjusting for history of trauma, sexual orientation, use of other substances, and family history of substance use. Cigarette use in adolescence and other drug use was associated with schizophrenia. This study demonstrates the importance of including potentially confounding factors when researching the association between cannabis use and schizophrenia (Ryan et al., 2020). These results contradict a slightly earlier study which used a genetic approach to demonstrate a causal relationship between cannabis use and schizophrenia even when accounting for cigarette smoking (Vaucher et al., 2018). As more locations legalize cannabis use the need for research to clarify the causal association between cannabis use and schizophrenia becomes increasingly important. Until more is known it would remain prudent for clinicians to advise against the use of cannabis before or during adolescence and young adulthood, especially if other risk factors are present and there is a family history of schizophrenia. Some good news is that patients suffering a first episode of psychosis who then stopped using cannabis, were able to reverse the worsening of schizophrenic symptoms that could be attributed to cannabis use. This suggests that intervention efforts aimed at getting patients with first episode psychotic breaks, and perhaps individuals with more established schizophrenia, to stop using cannabis could reduce the severity of the disease (Setién-Suero et al., 2019).

7. The Role of Stress, Geography, and Birth Conditions

Stress may play a role in the development of schizophrenic disease (Gomes & Grace, 2018). Immigration and migration, which are highly stressful, are known to increase risk of schizophrenia (Dykxhoorn et al., 2019; Henssler et al., 2020). Elevated prevalence of schizophrenia has been demonstrated in both current and past immigrant populations (Fearon et al., 2006; Henssler et al., 2020; Leão et al., 2006; Shekunov, 2016). Second generation immigrants are also at increased risk for schizophrenia (Bhugra, 2000). A study of Holocaust survivors demonstrated that pre-natal and early life exposure to adversity resulted in a significantly greater risk of developing schizophrenia (Butler et al., 1994).

Researchers have shown a relationship between prevalence of schizophrenia and latitude (Saha et al., 2006). Although a difference in rates of schizophrenia has been noted between developed and developing nations (Bresnahan et al., 2003) and a higher incidence of schizophrenia has been associated with developed nations, economic status of a country by itself was not predictive of incidence of the disease (Saha et al., 2006). However, inequality among the most socio-economically deprived has been associated with an increased incidence of schizophrenia (Peltzer, 1999).

Some research has suggested that season of birth may be related to the development of schizophrenia later in life. This seasonality may be a proxy for stress as well as infection status, maternal hormone levels, sperm quality, etc. (Tochigi et al., 2004). Other research has shown that a mother's pregnancy and birth conditions themselves have a moderate association with the development of schizophrenia in her offspring. Lack of contact with health care professionals, premature birth, infection with influenza virus, preeclampsia, hemorrhage during birth, manual extraction of the baby during delivery, and maternal sepsis during childbirth and the puerperium, all increased the risk of subsequent development of schizophrenia in the offspring. Interestingly, the greatest risk shown in this study was from infection of the mother by the influenza virus (Byrne et al., 2007). Severe obstetric complications have been shown to be related to lower IQ and the development of schizophrenia. It is thought that obstetric complications should be considered as a neurodevelopmental risk factor for severe mental illness (Wortinger et al., 2020).

8. Infectious Disease as a Cause of Schizophrenia

A number of infectious agents have been theorized to cause or trigger the onset of schizophrenia. This theory gained some prominence in the 20th century, with physicians noting the increase in cases of psychosis after the influenza pandemic of 1918 (Hendrick, 1928). Around the turn of the century the so-called 'focal sepsis' theory of mental illness became popular in Europe and the United States. Psychiatrists were eager to identify and treat

(often through surgery) mental illness through the eradication of infection just as physicians were doing successfully in many other areas of medicine. The use of surgical eradication of bacteria to cure mental illness is documented by Scull in the book *Madhouse: A Tragic Tale of Megalomania and Modern Medicine* (2005). In the early 20th century Dr. Henry A. Cotton, a noted psychiatrist and director of a mental hospital in New Jersey, promoted the surgical removal of body parts in order to 'remove' the infection that he was certain caused psychosis and other mental illness in his patients. The organs Dr. Cotton ordered removed included the cervix, gall bladder, ovaries, sinuses, spleen, stomach, teeth, testicles, and tonsils. Dr. Cotton was especially worried about the colon and this organ was often the target of his infection elimination surgery. Many hundreds of patients underwent unnecessary and dangerous surgeries (in pre-anti-biotic times) because of Dr. Cotton's obsession about the infectious causation of severe mental disease. Dr. Cotton reported very high success rates; upwards of 85%. However, these rates were largely anecdotal, and he didn't mention the very high rates of morbidity from the surgeries, not to mention their debilitating effects among the survivors (ironically enough, most morbidity and mortality from the surgeries were due to postoperative infections which were common in the pre-antibiotic era). Dr. Cotton even had his sons' teeth removed in order to prevent them from being infected as a preventative measure to insure their mental health. He also subjected his youngest son to abdominal surgery as a prophylaxis against mental illness and eventually convinced his wife to have all her teeth removed. Dr. Cotton's positive results for treating mental disease through focal sepsis could not be replicated by other researchers. Two very damming reviews of his research and methods were completed, but never disseminated. While Dr. Cotton's work was investigated and prominent psychiatrists involved with the investigation knew the uselessness of his treatment methods, his career remained largely unaffected. He continued in his post until his retirement, after which there was a marked reduction at least in abdominal surgery. The removal of focal sepsis as a treatment for mental disease did not fall out of favor until other treatments such as lobotomy came on the scene (Scull, 2005).

Because of clinicians like Cotton, infection as a causative factor in schizophrenia and psychoses fell out of favor. However, using much more sensitive tools, medicine is turning again to this line of research. Researchers have now proposed that there may indeed be infectious agents that directly affect the development of schizophrenia or, trigger autoimmune reactions that may be related to the disorder (Potvin et al., 2008). Potential schizophregenic infectious agents include *cytomegalovirus*, *herpes simplex virus* (HSV 1 & 2) and T. gondii (a parasitic protozoa commonly found in house cats) as well as influenza viruses. Dickerson et. al. (2006) found a relationship between the presence of antibodies to cytomegalovirus and 'deficit' schizophrenia (i.e. schizophrenia with a preponderance of negative symptoms). She did not find any relationships between other viruses and schizophrenia.

T. gondii is a neurotropic protozoan parasite that infects over a billion people around the world. Most people do not notice any ill effects from the parasite although it can cause complications in pregnancy including miscarriage, premature labor, stillbirth, and fetal abnormalities (Rashno et al., 2019). There have been numerous studies showing a relationship between T. gondii infection and risk for schizophrenia (Dickerson et al., 2007; Xiao et al., 2018). Best estimates from numerous studies indicate that T. gondii infection results in an almost 2.7 times increase in risk for developing schizophrenia compared to non-infected people (Torrey et al., 2012). A genome wide association study found a number of genes associated with T. gondii infection were related to neurodevelopment and psychiatric disorders, especially schizophrenia (A.W. Wang et al., 2019). Niebuhr and colleagues (2008) found a significant positive association between T. gondii antibodies and diagnosis of schizophrenia among military personnel. Interestingly T. gondii infection has been shown to be related to a number of risk-taking behaviors ranging from dangerous driving, suicide attempts, and risky sexual pursuits (Flegr & Kuba, 2016; Sutterland et al., 2019). It may that T. gondii-induced neuronal changes that can cause an escalation in risk-taking behavior may be related to an increased risk of developing schizophrenia.

Studies in Sweden found that viral infection of the central nervous system conferred a slight increased risk of developing schizophrenia and non-affective psychoses while bacterial infection did not. The later development of psychotic illness was specifically associated with the mumps or cytomegalovirus. The authors concluded that there was an association of severe viral central nervous system infection in childhood to viruses that can invade the actual brain tissue (Dalman et al., 2008; Khandaker et al., 2012). Some studies have suggested that the interaction of genes known to have variations related to schizophrenia and viral infection could increase the likelihood of schizophrenia (Beraki et al., 2005). Human respiratory coronaviruses are also known to infect the nervous system.

Therefore, it is possible that there could be a future increase in schizophrenia due to the COVID-19 pandemic (Cowan, 2020; Zandifar & Badrfam, 2020).

Prefrontal cortical structures in the brain have been found to be different among people with schizophrenia depending upon herpes simplex virus 1 (HSV-l) seropositivity (Prasad et al., 2007a). On first-diagnosis, patients suffering from schizophrenic and schizoaffective disorders who were exposed to HSV1 had decreased gray matter in the dorsolateral prefrontal cortex and anterior cingulate cortex when compared to patients suffering from schizophrenia who were not exposed to HSV1. Differences in brain structure that were related to HSV-1 exposure were not found among healthy control subjects. This suggests that HSV1 exposure may be related to changes in brain morphology commonly associated with schizophrenia, independent of medication use, co-morbid chronic illness, and substance abuse (Prasad et al., 2007b).

Animal models have demonstrated the theoretical possibility of pre-natal induced schizophrenia in offspring through a mimicked viral infection (Moreno et al., 2011). Studies in humans have suggested that pre-natal exposure to infectious agents appear to contribute more to subsequent development of schizophrenia than post-natal exposure. In humans, actual viral infection has not been definitively shown to directly cause schizophrenia in the offspring of infected mothers, but there is increasing evidence that it is a contributing factor. For instance, maternal exposure to HSV-2 has been theorized to cause schizophrenia and schizoaffective disorders. Yet, a study by Brown et. al (2006) did not find any support for a relationship between HSV-2 and subsequent schizophrenia and schizoaffective disorder in the offspring of infected mothers. On the other hand, a case-control study, did show a significant increased risk for the development of psychoses among offspring of mothers who had been exposed to HSV-2 (Buka et al., 2008). The risk was even greater if the mothers had high rates of sexual activity during their pregnancy. A study in mice suggests that a disruption of the balance of cytokines in mothers during gestation may lead to neurodevelopmental problems in their offspring (Meyer et al., 2008; Meyer et al., 2006, 2008). Another study with rats has shown that malnourishment in mothers is related to pro-inflammatory factors that may increase the risk of schizophrenia among their offspring (J. Xu et al., 2015). Fatemi et. al. (2008) examined the effects of maternal infection in mice with subsequent effects on brain structure and function in mice. They showed that infection near the end of the second trimester of pregnancy could lead to abnormal gene expression in the brain and subsequent structural defects that could be related to schizophrenia and autism. Mittal et. al. (2008) found that adolescents diagnosed with schizotypal personality disorder who had prenatal exposure to a viral teratogen were at increased risk for developing schizophrenia when compared to a similar group who did not have exposure. They conclude that the risk of psychosis is increased among the offspring of infected mothers. However, they note that mothers of high-risk children tended to over report exposure to infectious disease.

9. Autoimmune Hypothesis of Schizophrenia

In the 1980s, it was proposed that autoantibodies affected neurons in the limbic region of the brain, thereby causing schizophrenia (Knight, 1982). There is now an increasing amount of evidence that supports the idea that schizophrenia may be an autoimmune disease (Severance et al., 2016). A recent study found that the genes responsible for producing the cytokine Interleukin-8 (IL-8) were highly expressed in people suffering from schizophrenia causing greater production of the cytokine when compared to a control group. The results suggest that IL-8 could be responsible for pathophysiological changes in the brain that occur in people suffering from schizophrenia (L. Xu et al., 2018).

Lending credence to the autoimmune hypothesis of schizophrenia, another study found that the presence of many autoimmune diseases increased the risk of developing schizophrenia. Specifically, people suffering from systemic lupus erythematosus had 3.73 times more risk of developing schizophrenia. People suffering from rheumatoid arthritis had 2.89 times increase in risk and those with dermatomyositis had 5.85 times the risk of developing schizophrenia respectively. This contradicts reports that did not find an association between arthritis and schizophrenia (Cullen et al., 2019). Autoimmune vasculitis increased risk of developing schizophrenia by 2.44 times. This study also found that steroid use protected against developing schizophrenia (L-Y. Wang et al., 2018).

Other researchers conducted a meta-analysis of research on the relationship between non-neurological autoimmune (NNAI) disorders and psychoses. They found an overall positive relationship between NNAIs and

psychoses. Those with NNAIs were 1.26 times more likely to develop a psychosis. However, the specific disorders differed from the previous study cited above. People suffering from pernicious anemia and those with pemphigoid had 1.9 greater odds of becoming schizophrenic, while those with psoriasis, celiac disease, and Graves' disease had 1.7, 1.5 and 1.3 greater odds, respectively, of having schizophrenia. On the other hand, those suffering from ankylosing spondylitis and rheumatoid arthritis had about 0.7 decreased odds for developing the disorder. It is possible that inflammatory pathways, genetics, autoantibodies targeting brain proteins, and exposure to corticosteroids underlie the observed associations (Cullen et al., 2019).

A study of the connection between the genetics of autoimmune disorders and schizophrenia did not find genetic overlap in common single nucleotide polymorphisms which could explain co-morbidity in autoimmune disorders and schizophrenia (Hoeffding et al., 2017). The role of gastrointestinal disorders has been examined as a link between autoimmune disorders and schizophrenia (Severance et al., 2015). It is hypothesized that exposure to wheat gluten and bovine milk casein creates gut inflammation and humeral immunity to food antigens, which occurs early during the course of schizophrenia. The gut inflammation can increase gut permeability which allows gut bacteria to translocate into the circulatory system. This can trigger innate immunity including activation of C1q, which also functions in brain synapses. T. gondii infection is also known to initiate gut inflammation and could affect activation of immune responses in the brain in the same way. Immigrants, who are known to be at greater risk for schizophrenia, may be forced to modify their diets in a way which promotes gut inflammation and immune system activation affecting the brain. The authors conclude that an understanding of the disrupted microbiome can provide useful models of brain pathogenesis (Severance et al., 2016). A better understanding of the role of gut pathogens, the microbiome and their effects on the brain could lead to immunologic and microbial methods of prevention and treatment (Severance & Yolken, 2020).

10. Neurobiology of Schizophrenia

Much research is focused on the role of neurobiology in schizophrenia. However, the relationship of neurobiology to understanding the causes of the disease is still being debated (Brambilla & Tansella, 2007). While neurobiology is undoubtedly important, it is thought that the etiology of schizophrenia is multi-factorial (K. Dean et al., 2003).

The neurotransmitter dopamine has long been suspected as a key component of schizophrenic pathology. The so-called 'dopamine hypothesis' of schizophrenia grew from the observation that drugs that increase the activity of dopamine in the brain can also induce psychosis. Conversely drugs that block dopamine receptors were found to reduce psychotic symptoms (Baumeister & Francis, 2002). Briefly, the dopamine hypothesis asserts that in normal people the prefrontal dopamine system controls the limbic dopamine system through suppression. In individuals suffering from schizophrenia the activity of the dopaminergic neurons in the pre-frontal dopamine system is reduced causing overactivity of the limbic dopamine system. The reduced activity of the prefrontal dopamine neurons is responsible for the negative symptoms of schizophrenia while the overactivity of the limbic basal ganglia dopamine system is responsible for the positive symptoms of the disease. (Gründer & Cumming, 2016; Ohara, 2007).

Some studies have demonstrated increased dopaminergic activity in the mesolimbic pathway of the brain as well as abnormalities in cortical cholinergic transmission in people with schizophrenia (Masciotra et al., 2005; Sarter et al., 2005). Other neurotransmitters may work in concert with dopamine to form the basis of schizophrenic pathology. In normal people the action of dopamine is mediated by receptors on pyramidal and local circuit neurons that stabilize cortical representations of external and internal stimuli. In people with schizophrenia this mediation effect may be reduced, and along with dysfunction in gamma aminobutyric acid (GABA) and glutamate transmission, may contribute to cortical dysfunction (Winterer, 2006).

A number of studies suggest that dysfunction in the neurotransmitter GABA may be important in understanding schizophrenia. Abnormal GABA transmission in the brain may be related to cognitive, affective, sensory and motor problems in people with schizophrenia. A study assessing expression levels of GABA-related genes in the dorsolateral prefrontal cortex, anterior cingulate cortex (ACC), primary motor cortex, and primary visual cortex found reduced gene expression among subjects suffering from schizophrenia when compared to healthy controls. The authors concluded that since the areas studied represent major functional areas of the cortex, abnormality of

GABA transmission may be a contributing factor to a number of different schizophrenic symptoms (Hashimoto et al., 2008). An imaging study using proton magnetic resonance spectroscopy found lower levels of GABA in the ACC and frontal cortex of patients suffering from schizophrenia when compared to healthy control subjects. These differences were especially pronounced in first episode patients with schizophrenia (Kumar et al., 2020).

Some speculation related to the dopamine hypothesis suggests an important role for the N-methyl-D-aspartate (NMDA) receptor for the neurotransmitter glutamate, as these receptors regulate dopamine neurons in the cortex. Inhibition of the functioning of these receptors can bring about both the positive and negative symptoms of schizophrenia. This NMDA receptor hypofunction hypothesis of schizophrenia is supported by the observation that drugs like PCP, which reduce NMDA function, cause both negative and positive schizophrenic symptoms (Jentsch & Roth, 1999). Nevertheless, there are still issues to be worked out with this approach (Gilmour et al., 2012). There is some evidence that GABA-A receptors are disrupted in patients suffering from schizophrenia. There is some clinical evidence that when benzodiazepines, which act on GABA-A receptors, are administered with antipsychotic medications, better therapeutic outcomes are achieved than with antipsychotic medication alone (Włodarczyk et al., 2017).

There is an increasing amount of evidence that points to the role of limbic-corticostriatal glutamate transmission pathology as an underlying basis for schizophrenia. A review of the literature by Szumlinski & Kippin (2008) lists six findings that support this theory: smaller cortical volumes, reduced glutamatergic unmyelinated neuronal processes, fewer dendritic spines, pyramidal cell disarray, expression alteration in glutamate receptor subtypes, and reduced expression of cortical synaptic proteins. They go on to explain that the mainstream view is that these glutamate abnormalities in schizophrenia cause hypofrontality, or a reduction in cortical activity and activation. The authors also note that there are other theories that hold the opposite view; i.e. that glutamate hyperactivation caused by a disinhibition of glutamate transmission underlies the psychotic and cognitive abnormalities present in schizophrenia.

Serotonin receptor pathology in the cortex has been hypothesized to be associated with schizophrenia and other illnesses such as bi-polar disorder. Alteration of serotonin receptors may be subtle and may differ according to gender (Gray et al., 2006). Studies examining the contribution of genetic variation of serotonin-related receptors to schizophrenia have indicated that certain alleles, as well as the synergy among different alleles, may increase susceptibility to schizophrenia (Lorenzo et al., 2006). Serotonin (5-HT) function, which is known to be related to aggressive behavior in general, may also be related to aggressiveness among people suffering from schizophrenia (Barkan et al., 2006).

Other serotonin receptors may play a role in schizophrenia. Dean and his colleagues have shown that decreased levels of serotonin-sub-7 receptors in Brodmann's area 9 may be related to schizophrenic pathology in a post-mortem study of patients suffering from schizophrenia and in rats. These results are supported by the fact that cortical serotonin-sub-7 and -sub(1D) receptors are affected by antipsychotic drugs among individuals suffering from schizophrenia (Barkan et al., 2006; B. Dean et al., 2001, 2006). Additional studies have found that variations in serotonin transport related genes may be associated with increased susceptibility to schizophrenia as well as suicidal behavior among individuals suffering from schizophrenia (De Luca et al., 2006; Fan & Sklar, 2005). Antipsychotic drugs which are partial agonists to serotonin-5-HT-sub(1A) receptors, have improved cognition, including attention, executive function, verbal learning, and memory in some studies with patients suffering from schizophrenia (Sumiyoshi et al., 2007). Other drugs targeting serotonin reuptake inhibition have not been definitively shown to be useful in treating the negative symptoms of schizophrenia. A meta-analysis examining well-designed studies found that the negative symptoms of schizophrenia did not improve when medication was augmented with serotonin reuptake inhibitors. While some studies have shown alterations in the 5HT-sub(1a) receptor binding parameters in schizophrenia patients at post-mortem, a study with living patients did not find any relationship between schizophrenic symptoms and 5Ht-sub(1a) binding (Sepehry et al., 2007). Therefore, there is some question about the role of 5HT-sub(1a) receptors in the pathophysiology of schizophrenia (Frankle et al., 2006). Other studies have not found any association between 5-HT receptor polymorphism and schizophrenia (Kapelski et al., 2006).

11. Brain Structure and Schizophrenia

The ACC has been identified as a key area in the pathology of schizophrenia. Most studies of the ACC have focused on fairly simple measurements such as volume when comparing individuals suffering from schizophrenia to normal controls. One study using case control methodology and a novel scanning method was able to show reduced bilateral thickness in the paralimbic region of the ACC along with increased surface area in both the limbic and paralimbic ACC among subjects suffering from schizophrenia. No differences were found in grey matter volume, surface curvature, or central sulcus depth. This study illustrates the rapidly increasing sophistication of brain structure studies of schizophrenia (Fornito et al., 2008).

Limbic system pathology has become one of the focal areas of research in schizophrenia. Limbic areas of the brains in adults suffering from schizophrenia differ consistently from healthy people, but areas outside the limbic system also show differences. Children and adolescents with schizophrenia, however, tend to just have differences in the limbic system as opposed to the whole brain. This has led to the hypothesis that brain pathology associated with schizophrenia starts in the limbic system and then spreads over time. It also may be the case that the limbic pathology is just be part of a more global brain abnormality (White et al., 2008).

A number of studies have now shown that people suffering from schizophrenia have both anatomical and functional brain-wide connection dysfunction when compared to healthy people. These dysfunctions are thought to be the main mechanism for the pathophysiology of schizophrenia (Wotruba et al., 2014). One study found a decrease in the connections within and between limbic structures. There was also observed reduction in fibers connecting to the left fronto-temporal region in people suffering from schizophrenia when compared to healthy subjects. This is thought to be evidence for the fronto-temporal dysconnectivity hypotheses of the pathogenesis of schizophrenia (Ottet et al., 2013).

Research using functional magnetic resonance imaging (fMRI) has been used to compare resting state effective connectivity (rsEC) and resting state functional connectivity (rsFC) in people suffering from schizophrenia with healthy control subjects. Seventeen disruptions in rsEC were found in patients suffering from schizophrenia. These rsEC disruptions were associated with the thalamus and pathways from the limbic areas (including the hippocampus, parahippocampus, and cingulate cortex) to the thalamus. Among patients suffering from schizophrenia rsFC abnormality was found to be distributed throughout the whole brain. Since rsEC provides information about the directionality of connections in the brain, the idea that schizophrenia can be characterized by disruptions in the limbic areas that spread to the thalamus is not far-fetched. It should be possible to use rsEC and rsFC patterns in combination as diagnostic markers for schizophrenia (Hua et al., 2020).

A recent systematic review of the research literature by Gault et. al. (2018) provides much evidence that schizophrenia is caused by problems in the dopaminergic circuitry in the brain. The dopamine D receptor gene (DRD2) which exists in the highest quantities in the striatum, is part of the reward circuitry. Abnormalities related to the reward circuit have been associated with schizophrenia. Blockage of the DRD2 receptors by antipsychotic medication has been shown to normalize the reward circuitry and reduce schizophrenic symptoms. Because of the high concentrations of DRD2 in the striatum these areas of the brain could be targets for therapies that seek to normalize striatal dopaminergic circuitry. Also, abnormality in circuitry between the striatum and frontal and temporal lobes of the brain may contribute to negative and cognitive symptoms of schizophrenia. Structures that provide input to the striatum including the ventral tegmental area and hippocampus, as well as structures receiving signals from the striatum such as the basal ganglia, may also contribute to dopamine circuitry pathology. Based on the research literature, seven models of schizophrenia related dysfunction based on the above circuit abnormalities are hypothesized. These models suggest ~~that~~ intervention sites for new treatment technologies like deep brain stimulation (DBS).

12. Recent Findings Associated with Cognition and Schizophrenia

Cognitive impairment is key feature among people suffering from schizophrenia. In general, studies of cognition among people suffering from schizophrenia can be conceptualized into two areas, non-social and social cognition. Non-social cognition includes processing speed, verbal and visuospatial learning and memory, working memory,

attention/vigilance, and reasoning/problem solving. People suffering from schizophrenia demonstrate impairments in all of these cognitive domains as well as having impairments in perception. Studies of people with schizophrenia have shown that patterns of cognitive impairment in schizophrenia differ from other disorders such as dementia and bipolar disorders. The cognitive impairments that accompany schizophrenic illness have negative effects on how well people suffering from schizophrenia are able to function. Diminished functionality among people suffering from schizophrenia include the ability to take care of themselves, to work and hold down a job, and the ability to acquire important skills related to rehabilitation (Green et al., 2019). Antipsychotic medication is known to induce cognitive decline as well as other side effects related to greater morbidity and mortality (Agbeli, 2020). Moran et. al. (2020) compared cognitive performance among individuals with schizophrenia who were taking antipsychotic medication and not taking antipsychotic medication, with healthy subjects. Given the role of dopamine in reinforcement-based learning it was thought antipsychotic medication might be responsible for some cognitive deficit. The study found that both medicated and non-medicated subjects suffering from schizophrenia had pervasive cognitive deficits when compared to healthy subjects. Deficits were found in reinforcement learning, processing speed, cognitive control, working memory, verbal learning, and relational encoding and retrieval. This study demonstrates that cognitive deficits are attributable primarily to schizophrenic disease and not antipsychotic medication. However, another study by Albert et. al. (2019) found that patients suffering from schizophrenia who discontinued antipsychotic medication had better cognitive functioning that those who did not stop taking antipsychotic medication. Another study by Fu et. al. (2019) demonstrated that people suffering from schizophrenia who discontinued antipsychotic medication because of negative side effects had improved cognition. Many of these patients were then able to use active coping mechanisms to maintain their recovery. It may be that some patients suffering from schizophrenia have differing cognitive responses to antipsychotic medication depending on their genotype (Nelson et al., 2018).

It is likely that there are overlapping biological pathways in schizophrenia and normal cognitive ability. Genes associated with cognitive performance have been found to be related to genes associated with increased risk of schizophrenic disease. These genes play a role in neurotransmitter systems that are important to cognitive performance (Koch et al., 2020).

It may be the case that cognitive impairment in childhood can be predictive of later development of schizophrenic illness (Dickson et al., 2020). This is important because early identification of schizophrenic risk could help identify those who might benefit from interventions to improve cognitive abilities. Psychoeducational and therapeutic interventions have been shown to lessen the impact of cognitive impairment in people suffering from schizophrenia. It is not known if these interventions work on the social and functional impairments that result from cognitive impairment or whether the techniques work directly to improve cognitive impairment itself. Regardless, psychoeducational and therapeutic interventions have been shown to improve the quality of life for people suffering from schizophrenia (Maurel et al., 2011).

Sleep disorders are common among people who suffer from schizophrenia. Laskemoen et; al. (2020) found sleep disturbances among people with schizophrenia were related to cognitive impairment. Processing speed and inhibition, which are related to insomnia and hypersomnia, were associated with cognitive impairment in patients suffering from schizophrenia. This suggests that treating sleep disturbances may help cognitive functioning in people suffering from schizophrenia.

13. Social-Cognitive and Emotional Recognition Impairment in Schizophrenia

Burns (2007) in his book *The Decent of Madness*, presents an argument that schizophrenia is the by-product of the evolution of the human brain. The same genes that evolved to give humans a highly social brain are also responsible for the potential development of schizophrenia in our species. Enhanced social-cognitive skills gave early humans a huge fitness advantage and were therefore selected for during evolution even though, for a small percentage of the population, this genetic gift could go awry and cause schizophrenia. The ability to read emotional states in others is an important social-cognitive skill that has survival value for humans. Individuals suffering from schizophrenia are known to have difficulty in reading emotions in others, especially facial affect. A study by Gur, et. al. (2007) demonstrated that when patients diagnosed with schizophrenia performed an emotional identification task, they showed reduced activation of the limbic system compared to healthy controls. For healthy people correct

identification of threat-related facial expressions was associated with increased amygdala activation. Patients suffering from schizophrenia reacted just the opposite, showing decreased activation of the amygdala when confronted with threat expressions. When presented with fearful faces subjects suffering from schizophrenia responded with increased amygdala activation, but with a flat affect. The authors theorized this reaction might be related to overstimulation of the limbic system. They concluded that the abnormal activation of the amygdala in response to threat and fearful facial expression could lead to misidentification of emotions in others.

Another study examined subjects suffering from schizophrenia and normal subjects while they engaged in tasks involving intuitive and cognitive emotional conditions. When subjects suffering from schizophrenia performed the emotional recognition tasks the limbic areas of the brain related to processing of emotions failed to activate. Subjects suffering from schizophrenia showed reduced activation in areas of the brain related to holistic processing of facial features and instead showed increased activity in brain regions that analyze facial features. The results suggest that subjects suffering from schizophrenia lack the ability to intuitively read affect in others and compensate for this loss by using a more cognitive approach to identifying features related to emotions in others (Fakra et al., 2008). Another study examining gaze discrimination impairment found that subjects suffering from schizophrenia and healthy control subjects have similar gaze discrimination abilities. Yet the people suffering from schizophrenia showed reduced brain activity in areas related to executive, emotional and visual processing. When performing more difficult tasks, the healthy control subjects showed increased activation in the frontal and temporal regions of the brain. Increased activation was found in people suffering from schizophrenia when they were directly gazing at another face. The authors conclude that the results may be related to the problems people with schizophrenia have in interacting with other people (Kohler et al., 2008).

A study examining the disconnection of the autonomic arousal in the amygdala related to fear found individuals suffering from schizophrenia had abnormally increased arousal along with reductions in emotion-specific regions and the medial pre-frontal cortex. The authors concluded that when confronted with signals for danger the central and autonomic processing in people suffering from schizophrenia is disconnected. This type of dysfunction might be related to paranoid symptoms such as delusions (Williams et al., 2007). Some of this dysfunction could be related to suboptimal parental bonding in people suffering from schizophrenia. As mentioned above, people suffering from schizophrenia are more likely to have experienced childhood trauma and to have impairments in parental bonding and social cognitive skills. Physical neglect was found to be especially predictive of impairment in emotional recognition. However, optimal parental bonding attenuated the negative impact of childhood trauma on emotional recognition (Rokita et al., 2020).

14. Treatment of Schizophrenia

Historically, schizophrenia has been treated with a wide variety of modalities which were not especially effective. Trepanation, exorcism, beating, spinning, and hydrotherapy (immersion in both hot and cold water) were some of the early treatments for schizophrenia (Braslow, 1999; González de Chávez, 2009; Høyersten, 1996; Whitaker, 2002). Treatments such as immersion in water continued well into the modern era and could be brutal and dangerous[2].

Physical torment, especially in the form of beatings has dogged people suffering from schizophrenia throughout history (Whitaker, 2002). Like hydrotherapy, beating has only lately gone out of style even though it has long been outlawed. Beating was not so much a treatment but a form of patient management. Other forms of violence served as ways to manage patients into compliance while masquerading as treatments.

15. Neuromodulation

By the late 19th and early 20th centuries new treatments were being invented to treat schizophrenia and other severe mental illnesses. Primitive neuromodulation treatments in the form of convulsive therapies using insulin,

[2] My current position is at the site of a former mental hospital. When I first arrived, I was directed to go to an old hospital building which was being used as a warehouse where office furniture was being stored. There among the desks and chairs was a hydrotherapy apparatus that had been used with patients suffering from schizophrenia, presumably until the hospital had closed down in the late 1990s.

Cardiazol, Metrazol, and eventually electricity became routine for people suffering from schizophrenia. These forms of convulsive therapies were considered to reduce psychotic symptoms. Electroshock (ECT) became the preferred method because it was cheap and thought to be less dangerous than the other methods. ECT was thought to work by damaging the brain, causing the stripping away of the intellect. Psychotic symptoms were abated but this was short lived requiring further sessions and further damage to the brain. ECT could be especially dangerous when multiple sessions were administered over a short period of time. Strong muscle convulsions also caused bone breakage in up to 40% of patients (Whitaker, 2002).

While ECT is still used in psychiatry it has become much safer with the concurrent administration of muscle relaxants, lower current, and the use of ultra-brief pulsed stimulation which is not thought to cause permanent brain damage. Modern ECT is mostly used to treat pharmacoresistant mood disorders but has been used to treat schizophrenia as well. ECT is also used to treat schizophrenia in parts of the world where antipsychotics are not practical for financial reasons (Gazdag & Ungvari, 2019). There are positive anecdotal reports as to clinical effectiveness of treating schizophrenia with modern ECT though large studies are lacking (Rado & Hernandez, 2014). Research evidence is emerging for the effectiveness of modern ECT in treating pharmacoresistant schizophrenia. A small study by Thomann et. al. (2017) used modern ECT with pharmacoresistant patients suffering from schizophrenia and major depressive disorder (MDD) to research changes in brain structure and function. Right-sided unilateral ECT was found to change brain structure and function regardless of diagnosis. All patients in the study experienced improvement in their clinical symptoms. Seven patients suffering from MDD achieved remission and the other four experienced at least a 50% improvement. Four patients suffering from schizophrenia experienced at least a 50% improvement while the other five subjects experienced 25% improvement at minimum.

Other non-invasive methods of neuromodulation have been developed in recent years, but they are primarily used for treating mood disorders and are not thought to be as effective as modern ECT:

> *"Additional non-invasive therapies include magnetic seizure therapy, which focally induces the superficial cortex to produce seizures, repetitive transcranial magnetic stimulation, involving the pulse application of magnetic stimuli to alter cortical excitability, and vagal nerve stimulation, which sends electrical impulses to various brain regions via the solitary nucleus…The role for these alternative treatments remains unclear, as ECT is generally considered clinically superior."* (Staudt et al., 2019, p. 4)

Nevertheless, Poulet et. al. (2008) report that the use of transcranial magnetic stimulation (TMS) reduced resistant auditory hallucinations. A study by Fröhlich and Lustenberger (2020) speculates that non-invasive neuromodulation may be able to correct sleep abnormalities among people suffering from schizophrenia.
Rado and Hernandez (2014) report that TMS combined with a small amount of electric current shows promise in treating schizophrenia.

16. Psychosurgery

Beside convulsive therapies, the other treatment that was widely used to treat schizophrenia was psychosurgery. Staudt et. al. (2019) have given an excellent review of the history of psychosurgery and the section below is mostly drawn from their work. Burckhardt first reported performing the excision of regions of the brain with six patients. After being inspired by research on the removal of the frontal lobes in primates, Portuguese physicians Edgar Moniz and neurosurgeon Almeida Lima developed a procedure for creating lesions in the frontal lobes called a leucotomy. This was used to treat depression, anxiety, and aggression. In the United States the neurologist-neurosurgeon team of Walther Freeman and James Watts refined Moniz' procedure and renamed it the prefrontal lobotomy. A minimal form of the procedure was used for patients with affective disorders while a more invasive radical form was used for people suffering from schizophrenia. Freeman later adopted the technique of transorbital lobotomy which was developed by Italian psychiatrist Amarro Fiamberti. This technique involved sedating the patient with ECT, inserting an "ice-pick" like instrument through the orbital socket, and performing sweeping motions to destroy areas of the frontal lobes of the brain. This operation could be done by minimally trained physicians without the need for a surgeon or anesthesiologist and without the need for a specialized operating theater. Freeman ambitiously advocated for the technique and it became quite popular. Transorbital lobotomies

were performed throughout America and Europe. It is estimated that Freeman himself performed over 3000 procedures from the 1930s through the 1960s, with tens of thousands performed around the world (Caruso & Sheehan, 2017). Freeman claimed almost miraculous results from transorbital lobotomies, but as in many of the early treatments what counted as success was highly questionable and biased by the lack of scientific study. Some of Freeman's patients claimed long term improvement but this was not the majority. It is likely that patients had a very different view about what was considered a cure or improvement than many mental health professionals. For the latter, a positive outcome was anything that made patients easier to manage. The book *One Flew Over the Cuckoo's Nest* (Kesey, 1963) and subsequent film (Forman, 1975), dramatically illustrates this.

Freeman performed his last transorbital lobotomy in 1967 on a patient that had twice previously had the procedure. Unfortunately, he nicked a blood vessel and the patient died. Shortly thereafter, Freeman retired from practice and drove around the country in his recreational vehicle interviewing former patients about their positive experience with the operation. In is interesting to note that over time Freeman relaxed the indications for the transorbital lobotomy. He increasingly saw it as a panacea and by the end of his career he was lobotomizing children. In one notable case he lobotomized a 12-year-old boy who was having problems adjusting to the death of his mother and getting along with his stepmother (Dully & Fleming, 2007). Many physicians were not enthusiast about transorbital lobotomies and when the first antipsychotic medication, chlorpromazine (trade name Thorazine) became available (and marketed as a lobotomy in a bottle) it was enthusiastically adopted as the primary treatment for schizophrenia (López-Muñoz et al., 2005).

More precise forms of psychosurgery are still performed in very few cases but are mostly used to treat obsessive-compulsive disorder (Brakoulias et al., 2019). Nevertheless, the idea of using psychosurgery to treat schizophrenia has recently re-emerged, albeit in a far more subtle and less invasive forms. Deep brain stimulation (DBS) which involves placing an electrode which can deliver a small amount of current directly into the brain is now being proposed as a treatment for schizophrenia. In one study DBS was shown to prevent the emergence of sensorimotor gating, attentional selectivity, and executive functioning deficits in a rat model of schizophrenia (Hadar et al., 2018).

Gault et. al. (2018) review the growing interest in using neuromodulation via DBS to treat schizophrenia. As mentioned previously, they report on seven models of predominantly striatal dysregulation that provide possible therapeutic targets. The authors report that DBS could be used to correct dysregulation in these target circuits as well as treat areas of the brain related to tardive dyskinesia (a side effect from antipsychotic medication) and negative and cognitive symptoms of schizophrenia. Highlights of their research reports include the following studies:

In two reports where DBS was used in the ventral cortex and ventral striatum. The first report was a patient who suffered from OCD and residual schizophrenic symptoms. While the negative symptoms of schizophrenia did not change for this patient, their OCD symptoms and psychosocial functioning improved 25%-58%.

The second patient who suffered from schizophrenia was part of a clinical trial using DBS to alleviate symptoms in treatment-resistant schizophrenia. This study used a protocol with patients randomized to receive DBS at either the medial prefrontal cortex or nucleus accumbens. DBS stimulation would then remain on for three months, after which responsive patients would be crossed over to either a stimulation on or stimulation off group. This was a small trial of eight planned patients. The one patient to finish the trial demonstrated a 62% reduction in positive symptoms and a 33% improvement in negative symptoms. This patient initially received bi-lateral stimulation after adjusting to unilateral left sided stimulation. However, bilateral stimulation caused akathisia and the patient was returned to unilateral stimulation which resulted in a relapse of negative symptoms. Positive symptoms remained improved.

Another trial is slated to target the pars reticulata of the substantia nigra in order to modulate activity in the basal ganglia, as well as the medial dorsal and lateral prefrontal cortex. This may normalize medial dorsal activity and improve both cognitive and positive symptoms of schizophrenia. Lastly, a trial that was to use DBS targeting the ventral striatum and ventral tegmental area closed due to an inability to enroll patients.

A prospective, non-control group study treated schizophrenia with capsulotomy. This therapy, which has been used for severe cases of treatment-resistant OCD, involves the bi-lateral destruction of brain tissue in the internal capsule. The study reported improvement in 74% of patients suffering from schizophrenia.[3]

In their review Gault et. al. (2018) argue that people suffering from schizophrenia should have access to the possible benefits of DBS, but also caution that patients suffering from severe schizophrenia may not have the capacity to consent to such an invasive procedure.

17. Antipsychotic Medication

Since the 1950s schizophrenia has been generally treated with a variety of antipsychotic medications that alleviate the symptoms of the disease, but not the underlying pathology. Most of these drugs work by suppressing dopamine activity in the brain, and because of this, have many serious side effects such as tardive dyskinesia (Baumeister & Francis, 2002). While newer antipsychotic medications also affect the function of other neurotransmitters (B. Dean et al., 2006; Hagiwara et al., 2008), dopamine targets still play a key role in the newer drugs that treat schizophrenia (Seeman, 2000). The fact that newer second-generation antipsychotic drugs do not seem to be more effective than first generation antipsychotic drugs supports the importance of dopamine as a target for medication (Lewis & Lieberman, 2008; Lieberman et al., 2005). Unfortunately, second generation antipsychotic medications also retain many of the side effects of the first-generation drugs (Divac et al., 2014). Nevertheless, dopamine agonist antipsychotic medications have the best evidence for effectiveness in treating schizophrenia (Tandon et al., 2010).

While treatment with antipsychotic drugs has been in existence for almost 70 years, there are still many important unanswered questions related using them to treat individuals with schizophrenic and other psychotic disorders. Questions related to choice of drug, dosage, when and if another drug should be tried, monitoring the effects of the drug treatment, and whether drugs can halt or slow the progression of the illness remain without definitive answers. While medicine in general has been moving towards 'evidence based' treatment, the treatment of people suffering from schizophrenia largely remains precedent and experientially based – i.e. based on what an individual physician was taught and what they intuit to be best for a given patient (Davis & Leucht, 2008; Kane & Leucht, 2008).

Many people who suffer from schizophrenia may need to be hospitalized at some time in their lives. Hospitalization allows the patient to stabilize and receive regular doses of medication and is generally short in duration. However, when medication compliance is poor, patients suffering from schizophrenia may de-stabilize once they leave the inpatient setting and require re-hospitalization. This creates a 'revolving door' through the mental health system. A recent study supports this view, demonstrating that patients suffering from schizophrenia who take their antipsychotic medication on a regular basis have fewer and shorter incidences of hospitalization (dosReis et al., 2008).

Most currently available antipsychotic medications are primarily effective against the positive symptoms of schizophrenia. Negative and cognitive symptoms have been more difficult to treat. So-called second generation or atypical antipsychotic drugs have not proven themselves to be more effective than first generation antipsychotic medications in dealing with these symptoms (Lieberman et al., 2005). It may even be the case that first generation antipsychotic drugs are superior to second generation antipsychotics (Foussias & Remington, 2010).

A review by Krogmann, et. al. (2019) outlines a number of mono and add-on therapeutic agents are now being examined for their ability to treat schizophrenia. Some of these drugs are targeted towards positive and negative symptoms, negative symptoms alone, and residual and treatment-resistant positive symptoms. These drugs include dopamine receptor 1, 2 and 3 (D1, D2, D3) agonists, 5-hydroxytryptamine (serotonin) receptor (5HT) agonists and

[3] Capsulotomy has been used for a number of years for people suffering with treatment resistant OCD. One study of 19 severe OCD patients receiving capsulotomy had 37% fully responded to the surgery (meaning their OCD scores improved by at least 35%), while 10% had a partial response (i.e. their OCD scores improved by 25%). Three patients achieved remission. More than half the patients did not respond. These patients had suffered severe OCD for a longer time. Capsulotomy is not without risk. Two patients in the study suffered permanent complications including paralysis and cognitive impairment (D'Astous et al., 2013). Given the success rate and risk of capsulotomy, DBS, which is thought to be just as effective, may be a more promising treatment.

inhibiters, a dopamine receptor 1-regulated NMDA (glutamate) receptor and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (glutamate) receptor (AMPA) agonists, phosphodiesterase 10A enzyme (PDE10A) inhibitors, trace amine-associated receptor 1 (TAAR1) agonists, a nitric oxide donor, a sigma2 receptor (which is highly expressed in malignant cancer cells) antagonist, an alpha1-adrenergic (which is involved in norepinephrine and epinephrine signaling) antagonist, and a D-amino acid oxidase (DAAO - which produces ammonia and hydrogen peroxide that affect the brain) inhibitor. In addition, a number of existing antipsychotic drugs have been reformulated into long lasting and injectable formulations to improve adherence to antipsychotic medication regimens. Lastly a μ-opioid receptor antagonist is being tested to reduce Olanzapine-induced weight gain, associated cardiovascular issues, and (one assumes) constipation. The clinical trial results for these new therapeutic agents has been mixed. While progress has been made, challenges remain in finding a balance between side effects and adherence to the medication regimen for dopamine modulating medications. With regard to non-dopamine modulating novel drugs the authors state:

> *"These studies will need to prove that, in fact, such non-dopamine modulating agents can improve negative symptoms while maintaining positive symptom stability, despite the removal of the prior dopamine modulating antipsychotic agent that at one point was needed to reduce schizophrenia symptoms."* (p. 63)

They conclude that despite an urgent need for better pharmacological agents to treat schizophrenia, these will likely not be forthcoming until the pathophysiology of the disease is better understood.

18. Anti-Inflammatory and Immunomodulating Agents

As described above, immunity, autoimmunity, and inflammation may play a role in schizophrenia. The evidence linking autoimmune disorders and schizophrenia suggests that immunosuppressive therapies might be helpful in treating schizophrenia (Chaudhry et al., 2015; Knight et al., 2007). However, immunosuppressive therapies have had mixed results. It does seem that at least some cases of schizophrenia have an immunological component and that prevention of immune triggers may be helpful for high risk populations (Richard & Brahm, 2012). Evidence exists indicating there are abnormalities in cell-mediated processed, acute phase proteins, cytokines, and intracellular mediators among people suffering from schizophrenia. One study found that pro-inflammatory cytokines are increased in the blood of schizophrenic patients. Antipsychotic medication was not found to be a confounding factor (B. Miller et al., 2011). C-reactive protein (CRP) may be a marker for low-grade neuroinflammation which can become chronic, damaging the microvascular system in the brain and reducing cerebral blood flow (B & Tk, 2014).

Maternal immune activation can lead to prenatal exposure of pro-inflammatory cytokines, which can in turn cause both acute and long-term changes in neurobehavioral development. These present possible pre-natal targets for reducing susceptibility for developing schizophrenia. Treatment targets include neuroprotection and functional enhancement to prevent abnormal structural and functional changes in the brain, reduction of oxidative stress and toxicity, reduction of pro-inflammatory cytokines, increase in anti-inflammatory cytokines, modulation of microglia function, and reduction of environmental stressors (Hong & Bang, 2020).

New treatments based on immunosuppression, immunomodulation, and neuroinflammation are theoretically promising but have yet been proven. Medications or substances that have anti-inflammatory, immunomodulation or neuroprotective effects could be repurposed. These include davunetide (an eight amino acid peptide with neuroprotective qualities), IFN-γ-1b (an interferon used to treat multiple sclerosis), mesenchymal stem cells (which can change microglia from an activated to an anti-inflammatory state), minocycline (an antibiotic with anti-inflammatory effects), monoclonal antibodies (which have anti-inflammatory effects), non-steroidal anti-inflammatory drugs (NSAIDS), omega 3 fatty acids (which have anti-inflammatory effects) and statins (which have anti-inflammatory effects). Other substances could include antioxidant supplements like N-acetylcysteine (which may be neuroprotective), herbal substances such as cannabidiol (the anti-inflammatory non-THC component of the cannabis plant), and foods thought to reduce inflammation. It is possible these could be used in combination and in conjunction with standard pharmacotherapies. It is also possible that optimal use of

antipsychotic medication could help reduce inflammation.[4] Also, targeting immune and anti-inflammatory therapies to specific bio-markers and specific clinical sub-groups could provide a more personalized, and hopefully, more effective approach to treating schizophrenia (Hong & Bang, 2020; Krogmann et al., 2019; Pandurangi & Buckley, 2020; Sommer et al., 2012).

The role of immunity in the development of schizophrenia continues to be a promising area of research not only for treating schizophrenia but also for its prevention (Dickerson et al., 2017). If a microbial trigger could be found for schizophrenia, it is possible that a vaccine could be developed against the trigger, thereby preventing the disease (Adams et al., 2012). Clearly, more research on the relationship between immunity, schizophrenia, and immunity-mediating treatments needs to be done.

19. Psychotherapeutic Approaches to Treating Schizophrenia

Supportive psychotherapy is sometimes offered to people with Schizophrenia; however, this is usually to help patients cope with the disease rather than treating the disease itself. A recent review found that supportive therapy was not any better than standard care and less helpful than a variety of psychotherapeutic approaches (Buckley & Pettit, 2007). However, supportive care in a group setting has been shown to be useful (Nightingale & McQueeney, 1996).

There is growing use of cognitive-behavioral therapy (CBT) with patients suffering from schizophrenia. This use of CBT is usually done in concert with the use of antipsychotic medication and has demonstrated a general reduction in symptoms with especially good results in reducing positive and residual symptoms and strengthening reality testing. Depression is also seen as amenable to treatment using CBT among people suffering from schizophrenia (Sudak, 2004; Turkington et al., 2003, 2004; Warman & Beck, 2003). CBT group therapy has also been tried with patients suffering from schizophrenia. Some studies have shown improvements in overcoming social phobia and depression, but the results are not definitive (Lawrence et al., 2006). Another study demonstrated a reduction in feelings of hopelessness and low self-esteem using CBT in a group setting with patients suffering from schizophrenia (Barrowclough et al., 2006). In a study of a single patient who suffered from schizophrenia and pathological gambling, CBT combined with medication awareness training was found to reduce the severity of psychotic and pathological gambling symptoms, as well as improve psychosocial functioning and dispositional mindfulness (Shonin et al., 2014). A study of 16 patients suffering from schizophrenia spectrum disorders examined the effects of a form of CBT that was manualized and adapted to psychotic patients. The researchers found a reduction of delusional symptoms as well as a decrease in depressive symptoms (Lamster et al., 2018). The effects of CBT tailored to treat insomnia was examined among patients suffering from schizophrenia and insomnia. This study examined three types of insomnia in patients suffering from schizophrenia; classic severe insomnia, insomnia with normal sleep duration, and insomnia with hypersomnia. Patients with classic severe insomnia showed marked improvement in total sleep time while patients suffering from schizophrenia with insomnia and hypersomnia showed reductions in total sleep time. Patients suffering from schizophrenia with insomnia but normal sleep duration had a blunted response to CBT (Chiu et al., 2018).

Jauhur et. al. (2014) conducted a meta-analysis of the effectiveness of CBT for people suffering from schizophrenia. This study pooled data from randomized trials, controlling for randomization, masking of outcomes, incompleteness of data, use of a control, and publication bias. Results demonstrated that the therapeutic effect of CBT is small. In a comment on this study Gold (2015) notes that the data do not show much relationship between positive therapeutic outcomes and the number of sessions. He even suggests that there may be an inverse relationship with better outcomes coming from fewer sessions. Meta-analytic studies are especially helpful because many CBT studies have small numbers and data pooled from multiple studies may provide better estimates of the effectiveness of CBT. In his book *CBT for schizophrenia: Evidence-based interventions and future directions* Steel (2013) gives an overview of CBT-based treatments that are likely to be helpful to people suffering

[4] However, a potential problem is that antipsychotic medication can cause global immunosuppression. While this effect could enhance the therapeutic effect of the medication for schizophrenia, it could make subjects suffering from schizophrenia more susceptible to diseases and complications related to further immune suppression (May, 1968; Pang et al., 2017).

from schizophrenia. He also makes the case for using specialized CBT protocols that are tailored to specific symptoms such as command hallucinations, violent behavior and PTSD.

20. Psychodynamic Approaches to Treating Schizophrenia

Freud believed that psychoanalysis could not be successfully used with patients suffering from schizophrenia, but that has not stopped psychodynamic psychotherapists from trying work with patients suffering from this disorder over the years. There are many examples of psychodynamic treatments with patients suffering from schizophrenia with some important examples presented below.

Freud's most famous follower, until he broke off to form his own form of analysis, Carl Jung, began his career treating patients with schizophrenia and later made valuable efforts to understand the symbolism which appeared in psychotic symptoms (Jung, 1925). Other of Freud's followers also attempted to at least understand schizophrenia following Freud's principles (Ferenczi & Jones, 1916). Tidd (1937) reported the successful psychoanalytic treatment of a patient we might now label as schizotypal. He went on to report on the use of psychoanalytic treatment with patients suffering from schizophrenia that had undergone shock (convulsive) therapies (Tidd, 1938). Weininger (1938), recommended modification of psychoanalytic technique to be more active during acute psychosis. Fromm-Reichmann (1939) maintained that psychoanalysts could develop and maintain workable relationships with patients suffering from schizophrenia and that successful psychotherapy requires understanding a different kind of transference phenomena. Fairbairn (1941), who was one of the principle figures in the British Object Relations School of psychoanalysis, proposed revisions to Freud's original libido theory in terms of the development of object relations. He also modified psychoanalytic techniques when working with patients suffering from schizophrenia. In the 1950s French psychoanalyst Gisela Pankow developed a technique she called dynamic structuring which combined working with clay, psychoanalysis, and phenomenological therapy to help patients suffering from schizophrenia (Valon, 2020). More modern analytic-based therapies have built on Pankow's work (Bonnigal-Katz, 2019). By the 1970s Searles (1986) greatly contributed to the psychoanalytic understanding of schizophrenia. He proposed a more direct analytic approach to working with patients suffering from schizophrenia. More recently Downing and Mills (2018) have compiled evidence-based psychodynamic approaches to treatment for individuals suffering from schizophrenia in outpatient settings.

These are just some of the psychoanalytic clinicians who have worked with patients suffering from schizophrenia over the last 100 years. Psychodynamic approaches to treating schizophrenia have waxed and waned over time. An influential, but deeply flawed study demonstrating that antipsychotic medication had as good results as analytic treatment had a huge negative impact on the use of psychodynamic therapies with patients suffering from schizophrenia (May, 1968). However, the psychoanalytic treatment in the study was provided by very poorly trained resident physicians and was clearly not up to the level of a properly trained analyst or psychodynamic therapist. Nevertheless, after the study was published, interest in using psychodynamic-related treatment for schizophrenia dropped precipitously (Stone, 1999).

Other past reviews have suggested the negative effects of psychodynamic treatment of patients suffering from schizophrenia (Mueser & Berenbaum, 1990). Nevertheless, there are some modern psychodynamic therapists and analysts who have done psychotherapy or even a modified form of psychoanalysis with psychotic patients with good success (Gibbs, 2007; Giovachinni & Boyer, 1980; Gottdiener, 2006; Grotstein, 2001, 2003; Kortegaard, 1993; V. Volkan, 1995; 2012) .Though not definitive, there is some positive evidence that a psychodynamic approach can be useful; even with long-term patients in an inpatient setting (Davenport et al., 2000). It is also thought that a psychodynamic understanding of schizophrenia can help improve treatment even when the treatment itself is not psychodynamic (Kline et al., 1992). Lucas (2003) suggests that psychodynamic approaches to treatment give clinicians a way in which to symbolically understand and communicate with their patients suffering from schizophrenia in a way that can help them make sense of their situation.

Most psychodynamic approaches to the treatment of schizophrenia assume that psychotic processes develop in early childhood and are related to either a withdrawal from the world or an inability to separate from being

psychically fused with a mother-figure (De Masi, 2020). This may be due to pathological neurobiology, structural changes in the brain, and/or pathogenic parenting (V. Volkan, 1995) .

Eecke (2019) advocates using a Lacanian form of treatment with patients suffering from schizophrenia. This approach follows Lacan's idea that people with schizophrenia are unable to integrate a 'third' in their personalities. The person suffering from schizophrenia has a psychic structure that is a dyad between the infant and an omnipotent mother. An ego-structuring technique is used to let such people perceive themselves outside of this dyad and allow them to discover themselves as a separate individual.

V. Volkan has written about people with a psychotic self-organization (2012; 1995). In his chapter Cat People Revisited he presents a case of a person with this a psychotic self-organization and how this relates to the hoarding of cats. Volkan makes the case that such individuals have an undifferentiated core self-representation that is infused with 'bad' or aggressive emotions which he deems an infantile psychotic self (V. Volkan, 1995). This psychotic self can be enveloped by a healthier self-representation allowing the person to function relatively normally. However, they can become psychotic if the healthier self is overwhelmed by the infantile psychotic self. Psychoanalysis can be used to help the patient modify the infantile psychotic self and achieve separation-individuation (Akhtar & Volkan, 2005).

It is interesting to note from the studies cited above that much of the work using psychodynamic approaches to working with patients suffering from schizophrenia is being done outside of the United States. France in particular has been pioneering psychoanalytic based therapies for use with people suffering from schizophrenia (Kapsambelis, 2019).

21. Non-Western and Novel Treatments for Schizophrenia

In a review of a number of small studies traditional Indian Ayurvedic medicine showed promise for treating schizophrenia but was not as effective as chlorpromazine in acutely ill people (Agarwal et al., 2007). It has been speculated that Ayurvedic medicine, which has traditionally been used to treat immunologic disorders, may have a positive effect on schizophrenia by acting on the immune system (Juckel & Hoffmann, 2018). An ayurvedic polyherbal formulation called *brahmi vati* was found to have anticonvulsant and memory enhancement properties, and to counter amphetamine-induced schizophrenia in mice. Brahmi vati has been used since ancient times to treat seizures and schizophrenic symptoms in India (Mishra et al., 2018).

Research on Traditional Chinese medicine suggests that Chinese herbal medicine may work well in combination with antipsychotic drugs (Rathbone et al., 2007). Patients receiving electroacupuncture along with electroconvulsive therapies were shown to have fewer schizophrenic symptoms than controls. In addition, patients receiving electroacupuncture showed reduced weight as well as reduction in headaches, insomnia, dry mouth, and electrocardiographic abnormalities (Jia et al., 2019).

Some studies have indicated that the brains of people suffering from schizophrenia have reduced levels of Omega-3 fatty acids and some think that this may explain the reduced dopamine activity of the prefrontal cortex as well as suggesting Omega-3 fatty acid supplementation as a possible treatment (Ohara, 2007). It may be possible that a subset of patients suffering from schizophrenia can benefit from niacin augmentation (X. J. Xu & Jiang, 2015). Exercise has been shown to improve both positive and negative symptoms of schizophrenia, as well as quality of life, hippocampal function and volume, and cognition (Girdler et al., 2019; Mitsadali et al., 2020; Sabe et al., 2020; Shimada et al., 2019).

22. Recovery from Schizophrenia

Before the advent of antipsychotic medication most people suffering from schizophrenia in the Western world were relegated to living in institutions or some type of asylum. With the advent of antipsychotic medication, it became possible for people suffering from schizophrenia to exert some control over their psychotic symptoms. However, treatment goals for people suffering from schizophrenia have moved beyond control over symptoms to regaining social and cognitive function and a better quality of life (Silva & Restrepo, 2019).

Hope and self-esteem have been found to contribute to the subjective sense of recovery among people suffering from schizophrenia suggesting that these should be promoted during recovery (İpçi et al., 2020). One dimension of recovery from schizophrenia is the feeling of not being dominated by psychotic symptoms. This feeling was found to be associated with time spent in self-directed and sustained exercise (Gonzalez-Flores, 2020). In a qualitative study of people suffering from schizophrenia subjects describe facing considerable challenges in functioning but also describe a sense of well-being and satisfaction with their lives. This was described as being related to the presence of trusting relationships with healthcare providers and therapeutic conversations, as well as antipsychotic medication, and family support (Møllerhøj et al., 2019).

Early intervention is thought to be related to better recovery from schizophrenia, especially among those who are experiencing a first psychotic episode (Azrin et al., 2015). One study found that while early intervention defined as shorter duration of untreated psychotic symptoms, had a positive effect on recovery from schizophrenia, other factors were needed to predict complete recovery. These factors included including higher education level, a longer period of employment, and planned medication discontinuation within three years together (Chan et al., 2019).

Therapeutic intervention and support play an important role in recovery, which is defined as a personal process of establishing a fulfilling and meaningful life along with a positive sense of identity. Recovery has been found to be promoted by cognitive therapy among individuals suffering from schizophrenia (Vidal & Huguelet, 2019). This demonstrates that psychotherapy can move beyond dealing with specific aspects of schizophrenic disease, to the enhancement of a person's life. A systematic review of cognitive-behavioral and other types of therapy demonstrate they have a positive effect on recovery from schizophrenia (Rakitzi et al., 2020). There a good deal of evidence that psychodynamic therapy and psychoanalysis can be an effective approach to helping patients suffering from schizophrenia achieve full recovery as well as increasing their sense of meaning in their lives (Angyal, 1950; Downing & Mills, 2018; Garfield & Mackler, 2013; Gibbs, 2007; V. Volkan, 1995).

There is still a long way to go in fostering recovery from schizophrenia. Available data indicate that about one in seven people suffering from schizophrenia are able to achieve functional recovery (Silva & Restrepo, 2019). The addition of various types of support, including family support, educational attainment, and psychotherapies could change recovery rates for the better. More research needs to be done on the effectiveness of these modalities on the improvement of recovery.

23. Prevention of Schizophrenia

While prevention of schizophrenia appears to be far-fetched on the surface, many of the latest findings about the disorder provide evidence that preventative approaches may be useful. Environmentally mitigated risk factors related to migration and immigration that are known to increase risk for schizophrenia could be targeted. Exposure to various types of infection could be mitigated or treated. Nutritional risk factors can easily be prevented if adequate and high-quality food supplies are available. Psycho-social stressors, cannabis use, and advanced paternal age, all of which are associated with increased risk for schizophrenia, can be altered to reduce incidence of schizophrenia (A. S. Brown & McGrath, 2011).

There is some evidence that prenatal nutritional deficits increase the risk of schizophrenia. Vitamin D, folic acid, and iron are the three micronutrients that are possibly related to the subsequent development of schizophrenia. Therefore, pre-natal supplementation may be protective against the disease (McGrath et al., 2011).

Maternal influenza, toxoplasmosis, and genital/reproductive infections are known to be related to increased risk of schizophrenia in offspring. Prevention of these infections in mothers should be a relatively straightforward and effective prevention strategy (A. Brown & Patterson, 2011).

Possible immunological triggers of schizophrenia, including things that cause gut inflammation and degradation of the gut biome can be avoided, especially among people known to at higher risk, for example first degree relatives of patients suffering from schizophrenia (Severance & Yolken, 2020).

24. Conclusion

Schizophrenia is an intense, and widespread mental illness. It has a complex epidemiology with serious co-morbidities and mortalities. The voluminous amount of research into the causes of schizophrenia has made tremendous progress in unraveling the disease. While we have a much more nuanced and detailed knowledge of the disorder, a definitive comprehensive understanding of schizophrenia has not emerged. Nevertheless, new knowledge about schizophrenia has begun to influence how the disorder is treated. In the past, convulsive therapies and psychosurgery were erroneously thought to be effective treatments for schizophrenia. These invasive and dangerous methods were used often and indiscriminately, causing a great deal of suffering. Recently, however, greater understanding of the brain, advances in medical technology, and the success of deep brain stimulation and psychosurgery for OCD, have sparked an interest in using these techniques to treat schizophrenia. Advanced imaging technology combined with precision surgery now allow for selective targeting of brain structures for neuromodulation via DBS or precise ablation of brain tissue in severe and treatment resistant cases of schizophrenia. These approaches, in an environment of ethical oversight, could lead to important insights about the control of schizophrenic symptoms, while providing treatment options in severe and intractable cases of schizophrenia. Nevertheless, for most people suffering from schizophrenia, dopamine modulating antipsychotic medications remain the predominant treatment modality. Both first- and second-generation antipsychotic medications, however, have a number of serious side effects and do not effectively treat the negative and cognitive symptoms associated with schizophrenia. As a result, novel antipsychotic medications and better medication delivery systems are being developed. Clinical trials have produced mixed results but there is some hope that some of these new approaches will prove as effective or better than previous antipsychotic drugs with fewer side effects. Nevertheless, definitively better antipsychotic pharmacological agents will likely not appear until the pathophysiology of schizophrenia is better understood. Another promising area of pharmacological treatment of schizophrenia is anti-inflammatory and immunomodulating agents. A number of these have been studied and there is promise that this approach alone or in conjunction with antipsychotic medication will provide a breakthrough in the treatment and understanding of schizophrenia. While pharmacology continues to be the primary mechanism for treating schizophrenia, psychotherapeutic treatments are showing promise in alleviating some of the debilitating effects of the disease. Newer psychotherapeutic techniques derived from cognitive-behavioral therapies are showing promise in improving the lives of people suffering from schizophrenia. Innovative formulations of psychodynamic therapies as well as more nuanced understanding of the developmental psychopathology of schizophrenia also show promise in helping to treat the disorder. Many psychotherapies have moved beyond the treatment of symptoms to a focus on recovery. Treatments derived from alternative medicine, as well methods of prevention are also being tried or are on the horizon. Even though recovery rates are still low, there is hope that newer therapies as well as the combination of different therapeutic approaches may allow more people suffering from schizophrenia to live happy and fulfilling lives.

References

Adams, D. D., Knight, J. G., & Ebringer, A. (2012). The autoimmune model of schizophrenia. *ISRN Psychiatry*, *2012*, 758072. https://doi.org/10.5402/2012/758072

Agarwal, V., Abhijnhan, A., & Raviraj, P. (2007). Ayurvedic medicine for schizophrenia. *The Cochrane Database of Systematic Reviews*, *4*, CD006867. https://doi.org/10.1002/14651858.CD006867

Agbeli, M. O. (2020). *Reducing antipsychotic medication use in long-term care settings* (2020-04052-126; Issues 5-A). ProQuest Information & Learning.

Akhtar, S., & Volkan, V. D. (2005). *Mental zoo: Animals in the human mind and its pathology*. International Universities Press.

Albert, N., Randers, L., Allott, K., Jensen, H. D., Melau, M., Hjorthøj, C., & Nordentoft, M. (2019). Cognitive functioning following discontinuation of antipsychotic medication A naturalistic sub-group analysis from the OPUS II trial. *Psychological Medicine*, *49*(7), 1138–1147. https://doi.org/10.1017/S0033291718001836

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition: DSM-5* (5 edition). American Psychiatric Publishing.

Angyal, A. (1950). The psychodynamic process of illness and recovery in a case of catatonic schizophrenia. *Psychiatry: Journal for the Study of Interpersonal Processes*, *13*, 149–165.

Arnaiz, A., Zumárraga, M., Díez-Altuna, I., Uriarte, J. J., Moro, J., & Pérez-Ansorena, M. A. (2011). Oral health and the symptoms of schizophrenia. *Psychiatry Research*, *188*(1), 24–28. https://doi.org/10.1016/j.psychres.2010.09.012

Ashcroft, K., Kingdon, D. G., & Chadwick, P. (2012). Persecutory delusions and childhood emotional abuse in people with a diagnosis of schizophrenia. *Psychosis: Psychological, Social and Integrative Approaches*, *4*(2), 168–171. https://doi.org/10.1080/17522439.2011.619012

Azrin, S. T., Goldstein, A. B., & Heinssen, R. K. (2015). Early intervention for psychosis: The Recovery After an Initial Schizophrenia Episode project. *Psychiatric Annals*, *45*(11), 548–553. https://doi.org/10.3928/00485713-20151103-05

B, S., & Tk, C. (2014). Role of C-reactive protein in schizophrenia: An overview. *Psychiatry Research*, *216*(2), 277–285. https://doi.org/10.1016/j.psychres.2014.02.004

Barkan, T., Peled, A., Modai, I., Barak, P., Weizman, A., & Rehavi, M. (2006). Serotonin transporter characteristics in lymphocytes and platelets of male aggressive schizophrenia patients compared to non-aggressive schizophrenia patients. *European Neuropsychopharmacology*, *16*(8), 572–579. https://doi.org/10.1016/j.euroneuro.2006.03.001

Barrowclough, C., Haddock, G., Lobban, F., Jones, S., Siddle, R., Roberts, C., & Gregg, L. (2006). Group cognitive-behavioural therapy for schizophrenia. *British Journal of Psychiatry*, *189*(6), 527–532. https://doi.org/10.1192/bjp.bp.106.021386

Baumeister, A. A., & Francis, J. L. (2002). Historical development of the dopamine hypothesis of schizophrenia. *Journal of the History of the Neurosciences*, *11*(3), 265–277. https://doi.org/10.1076/jhin.11.3.265.10391

Beraki, S., Aronsson, F., Karlsson, H., Ögren, S. O., & Kristensson, K. (2005). Influenza A virus infection causes alterations in expression of synaptic regulatory genes combined with changes in cognitive and emotional behaviors in mice. *Molecular Psychiatry*, *10*(3), 299–308. https://doi.org/10.1038/sj.mp.4001545

Bhugra, D. (2000). Migration and schizophrenia. *Acta Psychiatrica Scandinavica*, *102*, 68–73. https://doi.org/10.1034/j.1600-0447.2000.00015.x

Bonnigal-Katz, D. (2019). Psychosis Therapy Project: A psychoanalytic project in the community. *British Journal of Psychotherapy*, *35*(4), 586–589. https://doi.org/10.1111/bjp.12466

Boydell, J., Van Os, J., Lambri, M., Castle, D., Allardyce, J., McCreadie, R. G., & Murray, R. M. (2003). Incidence of schizophrenia in south-east London between 1965 and 1997. *British Journal of Psychiatry*, *182*(1), 45–49. https://doi.org/10.1192/bjp.182.1.45

Brakoulias, V., Starcevic, V., Albert, U., Arumugham, S. S., Bailey, B. E., Belloch, A., Borda, T., Dell'Osso, L., Elias, J. A., Falkenstein, M. J., Ferrao, Y. A., Fontenelle, L. F., Jelinek, L., Kalogeraki, L., Kay, B., Laurito, L. D., Lochner, C., Maina, G., Marazziti, D., … Fineberg, N. A. (2019). Treatments used for obsessive-compulsive disorder-An international perspective. *Human Psychopharmacology*, *34*(1), e2686. https://doi.org/10.1002/hup.2686

Brambilla, P., & Tansella, M. (2007). Can neuroimaging studies help us in understanding the biological causes of schizophrenia? *International Review of Psychiatry*, *19*(4), 313–314. https://doi.org/10.1080/09540260701507954

Braslow, J. T. (1999). History and evidence-based medicine: Lessons from the history of somatic treatments from the 1900s to the 1950s. *Mental Health Services Research*, *1*(4), 231–240. https://doi.org/10.1023/a:1022325508430

Bray, I., Waraich, P., Jones, W., Slater, S., Goldner, E. M., & Somers, J. (2006). Increase in schizophrenia incidence rates: Findings in a Canadian cohort born 1975-1985. *Social Psychiatry and Psychiatric Epidemiology*, *41*(8), 611–618. https://doi.org/10.1007/s00127-006-0073-z

Bresnahan, M., Menezes, P., Varma, V., & Susser, E. (2003). Geographical variation in incidence, course and outcome of schizophrenia: A comparison of developing and developed countries. *The Epidemiology of Schizophrenia.*, 18–33.

Brown, A. S., & McGrath, J. J. (2011). The Prevention of Schizophrenia. *Schizophrenia Bulletin*, *37*(2), 257–261. https://doi.org/10.1093/schbul/sbq122

Brown, A. S., & Patterson, P. H. (2011). Maternal Infection and Schizophrenia: Implications for Prevention. *Schizophrenia Bulletin*, *37*(2), 284–290. https://doi.org/10.1093/schbul/sbq146

Brown, A. S., Schaefer, C. A., Quesenberry, C. P. Jr., Shen, L., & Susser, E. S. (2006). No evidence of relation between maternal exposure to herpes simplex virus type 2 and risk of schizophrenia? *American Journal of Psychiatry*, *163*(12), 2178–2180. https://doi.org/10.1176/appi.ajp.163.12.2178

Brown, S., Inskip, H., & Barraclough, B. (2000). Causes of the excess mortality of schizophrenia. *British Journal of Psychiatry*, *177*, 212–217. https://doi.org/10.1192/bjp.177.3.212

Buckley, L., & Pettit, T. (2007). Supportive therapy for schizophrenia. *Schizophrenia Bulletin*, *33*(4), 859–860. https://doi.org/10.1093/schbul/sbm058

Buka, S. L., Cannon, T. D., Torrey, E. F., & Yolken, R. H. (2008). Maternal exposure to herpes simplex virus and risk of psychosis among adult offspring. *Biological Psychiatry*, *63*(8), 809–815.

Burns, J. (2007). *The Descent of Madness: Evolutionary Origins of Psychosis and the Social Brain* (1 edition). Routledge.

Butler, P. D., Susser, E. S., Brown, A. S., Kaufmann, C. A., & Gorman, J. M. (1994). Prenatal nutritional deprivation as a risk factor in schizophrenia: Preclinical evidence. *Neuropsychopharmacology*, *11*(4), 227–235. https://doi.org/10.1038/sj.npp.1380109

Byrne, M., Agerbo, E., Bennedsen, B., Eaton, W. W., & Mortensen, P. B. (2007). Obstetric conditions and risk of first admission with schizophrenia: A Danish national register based study. *Schizophrenia Research*, *97*(1), 51–59. https://doi.org/10.1016/j.schres.2007.07.018

Capasso, R. M., Lineberry, T. W., Bostwick, J. M., Decker, P. A., & St. Sauver, J. (2008). Mortality in schizophrenia and schizoaffective disorder: An Olmsted County, Minnesota cohort: 1950-2005. *Schizophrenia Research*, *98*(1), 287–294. https://doi.org/10.1016/j.schres.2007.10.005

Caruso, J. P., & Sheehan, J. P. (2017). Psychosurgery, ethics, and media: A history of Walter Freeman and the lobotomy. *Neurosurgical Focus*, *43*(3), E6. https://doi.org/10.3171/2017.6.FOCUS17257

Casey, D. E., Haupt, D. W., Newcomer, J. W., Henderson, D. C., Sernyak, M. J., Davidson, M., Lindenmayer, J.-P., Manoukian, S. V., Banerji, M. A., Lebovitz, H. E., & Hennekens, C. H. (2004). Antipsychotic-lnduced Weight Gain and Metabolic Abnormalities: Implications for Increased Mortality in Patients with Schizophrenia. *Journal of Clinical Psychiatry*, *65*, 4–18.

Castle, D. J., & Morgan, V. (2008). Epidemiology. *Clinical Handbook of Schizophrenia.*, 14–24.

Chan, S. K. W., Hui, C. L. M., Chang, W. C., Lee, E. H. M., & Chen, E. Y. H. (2019). Ten-year follow up of patients with first-episode schizophrenia spectrum disorder from an early intervention service: Predictors of clinical remission and functional recovery. *Schizophrenia Research*, *204*, 65–71. https://doi.org/10.1016/j.schres.2018.08.022

Chaudhry, I. B., Husain, N., ur Rahman, R., Husain, M. O., Hamirani, M. M., Kazmi, A., Baig, S., Haddad, P. M., Buch, M. H., Qureshi, I., Mehmood, N., Kiran, T., Fu, B., Afsar, S., & Deakin, B. (2015). A randomised double-blind placebo-controlled 12- week feasibility trial of methotrexate added to treatment as usual in early schizophrenia: Study protocol for a randomised controlled trial. *Trials*, *16*, 9. https://doi.org/10.1186/1745-6215-16-9

Cheniaux, E., Landeira-Fernandez, J., Telles, L. L., Lessa, J. L. M., Dias, A., Duncan, T., & Versiani, M. (2008). Does schizoaffective disorder really exist? A systematic review of the studies that compared schizoaffective disorder with schizophrenia or mood. *Journal of Affective Disorders*, *106*(3), 209–217. https://doi.org/10.1016/j.jad.2007.07.009

Chiu, V. W., Ree, M., Janca, A., Iyyalol, R., Dragovic, M., & Waters, F. (2018). Sleep profiles and CBT-I response in schizophrenia and related psychoses. *Psychiatry Research*, *268*, 279–287. https://doi.org/10.1016/j.psychres.2018.07.027

Chwastiak, L. A., & Tek, C. (2009). The unchanging mortality gap for people with schizophrenia. *The Lancet*, *374*(9690), 590–592. https://doi.org/10.1016/S0140-6736(09)61072-2

Cowan, H. R. (2020). Is schizophrenia research relevant during the COVID-19 pandemic? *Schizophrenia Research*. https://doi.org/10.1016/j.schres.2020.04.002

Cullen, A. E., Holmes, S., Pollak, T. A., Blackman, G., Joyce, D. W., Kempton, M. J., Murray, R. M., McGuire, P., & Mondelli, V. (2019). Associations Between Non-neurological Autoimmune Disorders and Psychosis: A Meta-analysis. *Biological Psychiatry*, *85*(1), 35–48. https://doi.org/10.1016/j.biopsych.2018.06.016

Dalman, C., Allebeck, P., Gunnell, D., Harrison, G., Kristensson, K., Lewis, G., Lofving, S., Rasmussen, F., Wicks, S., & Karlsson, H. (2008). Infections in the CNS during childhood and the risk of subsequent psychotic illness: A cohort study of more than one million Swedish subjects. *American Journal of Psychiatry*, *165*(1), 59–65. https://doi.org/10.1176/appi.ajp.2007.07050740

D'Astous, M., Cottin, S., Roy, M., Picard, C., & Cantin, L. (2013). Bilateral stereotactic anterior capsulotomy for obsessive-compulsive disorder: Long-term follow-up. *Journal of Neurology, Neurosurgery, and Psychiatry*, *84*(11), 1208–1213. https://doi.org/10.1136/jnnp-2012-303826

Davenport, S., Hobson, R., & Margison, F. (2000). Treatment development in psychodynamic-interpersonal psychotherapy (Hobson's 'Conversational Model') for chronic treatment resistant schizophrenia: Two single case studies. *British Journal of Psychotherapy*, *16*(3), 287–302. https://doi.org/10.1111/j.1752-0118.2000.tb00520.x

Davis, J. M., & Leucht, S. (2008). Has research informed us on the practical drug treatment of schizophrenia? *Schizophrenia Bulletin*, *34*(3), 403–405. https://doi.org/10.1093/schbul/sbn011

De Luca, V., Zai, G., Tharmalingam, S., de Bartolomeis, A., Wong, G., & Kennedy, J. L. (2006). Association study between the novel functional polymorphism of the serotonin transporter gene and suicidal behaviour in schizophrenia. *European Neuropsychopharmacology*, *16*(4), 268–271. https://doi.org/10.1016/j.euroneuro.2005.09.007

De Masi, F. (2020). Psychosis and analytic therapy: A complex relationship. *The International Journal of Psychoanalysis*, *101*(1), 152–168. https://doi.org/10.1080/00207578.2020.1716626

Dean, B., Hussain, T., Scarr, E., Pavey, G., & Copolov, D. L. (2001). Extended treatment with typical and atypical antipsychotic drugs: Differential effects on the densities of dopamine D-sub-2-like and GABA-sub(A) receptors in rat striatum. *Life Sciences*, *69*(11), 1257–1268. https://doi.org/10.1016/S0024-3205(01)01214-0

Dean, B., Pavey, G., Thomas, D., & Scarr, E. (2006). Cortical serotonin-sub(7, 1D) and -sub(1F) receptors: Effects of schizophrenia, suicide and antipsychotic drug treatment. *Schizophrenia Research*, *88*(1), 265–274. https://doi.org/10.1016/j.schres.2006.07.003

Dean, K., Bramon, E., & Murray, R. M. (2003). The causes of schizophrenia: Neurodevelopment and other risk factors. *Journal of Psychiatric Practice*, *9*(6), 442–454. https://doi.org/10.1097/00131746-200311000-00007

Dickerson, F., Boronow, J., Stallings, C., Origoni, A., & Yolken, R. (2007). Toxoplasma gondii in individuals with schizophrenia: Association with clinical and demographic factors and with mortality. *Schizophrenia Bulletin*, *33*(3), 737–740. https://doi.org/10.1093/schbul/sbm005

Dickerson, F., Kirkpatrick, B., Boronow, J., Stallings, C., Origoni, A., & Yolken, R. (2006). Deficit schizophrenia: Association with serum antibodies to cytomegalovirus. *Schizophrenia Bulletin*, *32*(2), 396–400. https://doi.org/10.1093/schbul/sbi054

Dickerson, F., Severance, E., & Yolken, R. (2017). The microbiome, immunity, and schizophrenia and bipolar disorder. *Brain, Behavior, and Immunity*, *62*, 46–52. https://doi.org/10.1016/j.bbi.2016.12.010

Dickson, H., Hedges, E. P., Ma, S. Y., Cullen, A. E., MacCabe, J. H., Kempton, M. J., Downs, J., & Laurens, K. R. (2020). Academic achievement and schizophrenia: A systematic meta-analysis. *Psychological Medicine*. https://doi.org/10.1017/S0033291720002354

Dion, G. L., & Dellario, D. (1988). Symptom subtypes in persons institutionalized with schizophrenia: Comparison of demographics, outcome and functional skills. *Rehabilitation Psychology*, *33*(2), 95–104. https://doi.org/10.1037/h0091684

Divac, N., Prostran, M., Jakovcevski, I., & Cerovac, N. (2014). Second-generation antipsychotics and extrapyramidal adverse effects. *BioMed Research International*, *2014*, 656370. https://doi.org/10.1155/2014/656370

dosReis, S., Johnson, E., Steinwachs, D., Rohde, C., Skinner, E. A., Fahey, M., & Lehman, A. F. (2008). Antipsychotic treatment patterns and hospitalizations among adults with schizophrenia. *Schizophrenia Research*, *101*(1), 304–311. https://doi.org/10.1016/j.schres.2007.12.475

Downing, D. L., & Mills, J. (2018). *Outpatient Treatment of Psychosis: Psychodynamic Approaches to Evidence-Based Practice*. Routledge. https://doi.org/10.4324/9780429478123

Dully, H., & Fleming, C. (2007). *My Lobotomy*. Crown.

Dykxhoorn, J., Hollander, A.-C., Lewis, G., Magnusson, C., Dalman, C., & Kirkbride, J. B. (2019). Risk of schizophrenia, schizoaffective, and bipolar disorders by migrant status, region of origin, and age-at-migration: A national cohort study of 18 million people. *Psychological Medicine*, *49*(14), 2354–2363. https://doi.org/10.1017/S0033291718003227

Eecke, W. V. (2019). How Does Psychoanalysis Work with Persons Afflicted By Schizophrenia? *Journal of Psychology & Psychotherapy*, *9*(5), 1–5. https://doi.org/10.35248/2161-0487.19.9.367

Enger, C., Weatherby, L., Reynolds, R. F., Glasser, D. B., & Walker, A. M. (2004). Serious Cardiovascular Events and Mortality Among Patients with Schizophrenia. *Journal of Nervous and Mental Disease*, *192*(1), 19–27. https://doi.org/10.1097/01.nmd.0000105996.62105.07

Fairbairn, W. R. D. (1941). A revised psychopathology of the psychoses and psychoneuroses. *The International Journal of Psychoanalysis*, *22*, 250–270.

Fakra, E., Salgado-Pineda, P., Delaveau, P., Hariri, A. R., & Blin, O. (2008). Neural bases of different cognitive strategies for facial affect processing in schizophrenia. *Schizophrenia Research*, *100*(1), 191–205. https://doi.org/10.1016/j.schres.2007.11.040

Fan, J. B., & Sklar, P. (2005). Meta-analysis reveals association between serotonin transporter gene STin2 VNTR polymorphism and schizophrenia. *Molecular Psychiatry*, *10*(10), 928–938. https://doi.org/10.1038/sj.mp.4001690

Fatemi, S. H., Reutiman, T. J., Folsom, T. D., Huang, H., Oishi, K., Mori, S., Smee, D. F., Pearce, D. A., Winter, C., Sohr, R., & Juckel, G. (2008). Maternal infection leads to abnormal gene regulation and brain atrophy in mouse offspring: Implications for genesis of neurodevelopmental disorders. *Schizophrenia Research*, *99*(1), 56–70. https://doi.org/10.1016/j.schres.2007.11.018

Fearon, P., Kirkbride, J. B., Morgan, C., Dazzan, P., Morgan, K., Lloyd, T., Hutchinson, G., Tarrant, J., Fung, W. L. A., Holloway, J., Mallett, R., Harrison, G., Leff, J., Jones, P. B., & Murray, R. M. (2006). Incidence of schizophrenia and other psychoses in ethnic minority groups: Results from the MRC AESOP Study. *Psychological Medicine*, *36*(11), 1541–1550. https://doi.org/10.1017/S0033291706008774

Ferenczi, S., & Jones, E. (1916). Some Clinical Observations on Paranoia and Paraphrenia. In *Contributions to psycho-analysis.* (2006-03526-011; pp. 238–249). Richard G. Badger. https://doi.org/10.1037/10925-011

Findlay, L. J. (2015). *Decision-making processes and health behaviors among adults diagnosed with schizophrenia* (2015-99060-062; Issues 9-B(E)). ProQuest Information & Learning.

Flegr, J., & Kuba, R. (2016). The relation of Toxoplasma infection and sexual attraction to fear, danger, pain, and submissiveness. *Evolutionary Psychology*, *14*(3). https://doi.org/10.1177/1474704916659746

Fonseca, L., Diniz, E., Mendonça, G., Malinowski, F., Mari, J., Gadelha, A., Fonseca, L., Diniz, E., Mendonça, G., Malinowski, F., Mari, J., & Gadelha, A. (2020). Schizophrenia and COVID-19: Risks and recommendations. *Brazilian Journal of Psychiatry*, *AHEAD*. https://doi.org/10.1590/1516-4446-2020-0010

Forman, M. (1975). *One Flew Over the Cuckoo's Nest*. Warner.

Fornito, A., Yücel, M., Wood, S. J., Adamson, C., Velakoulis, D., Saling, M. M., McGorry, P. D., & Pantelis, C. (2008). Surface-based morphometry of the anterior cingulate cortex in first episode schizophrenia. *Human Brain Mapping*, *29*(4), 478–489. https://doi.org/10.1002/hbm.20412

Fors, B. M., Isacson, D., Bingefors, K., & Widerlöv, B. (2007). Mortality among persons with schizophrenia in Sweden: An epidemiological study. *Nordic Journal of Psychiatry*, *61*(4), 252–259. https://doi.org/10.1080/08039480701414932

Foussias, G., & Remington, G. (2010). Antipsychotics and schizophrenia: From efficacy and effectiveness to clinical decision-making. *Canadian Journal of Psychiatry. Revue Canadienne De Psychiatrie*, *55*(3), 117–125. https://doi.org/10.1177/070674371005500302

Frankle, W. G., Lombardo, I., Kegeles, L. S., Slifstein, M., Martin, J. H., Huang, Y., Hwang, D.-R., Reich, E., Cangiano, C., Gil, R., Laruelle, M., & Abi-Dargham, A. (2006). Serotonin 1A receptor availability in patients with schizophrenia and schizo-affective disorder: A positron emission tomography imaging study with [^{11}C] WAY 100635. *Psychopharmacology*, *189*(2), 155–164. https://doi.org/10.1007/s00213-006-0543-8

Fröhlich, F., & Lustenberger, C. (2020). Neuromodulation of sleep rhythms in schizophrenia: Towards the rational design of non-invasive brain stimulation. *Schizophrenia Research*. https://doi.org/10.1016/j.schres.2020.04.003

Fromm-Reichmann, F. (1939). Transference problems in schizophrenics. *The Psychoanalytic Quarterly*, *8*, 412–426.

Fu, S., Czajkowski, N., & Torgalsbøen, A.-K. (2019). Cognitive, work, and social outcomes in fully recovered first-episode schizophrenia: On and off antipsychotic medication. *Psychiatry: Interpersonal and Biological Processes*. https://doi.org/10.1080/00332747.2018.1550735

Garfield, D., & Mackler, D. (2013). *Beyond Medication: Therapeutic Engagement and the Recovery from Psychosis*. Routledge.

Garver, D. L., Holcomb, J. A., & Christensen, J. D. (2000). Heterogeneity of response to antipsychotics from multiple disorders in the schizophrenia spectrum. *Journal of Clinical Psychiatry*, *61*(12), 964–974.

Gault, J. M., Davis, R., Cascella, N. G., Saks, E. R., Corripio-Collado, I., Anderson, W. S., Olincy, A., Thompson, J. A., Pomarol-Clotet, E., Sawa, A., Daskalakis, Z. J., Lipsman, N., & Abosch, A. (2018). Approaches to neuromodulation for schizophrenia. *Journal of Neurology, Neurosurgery & Psychiatry*, *89*(7), 777–787. https://doi.org/10.1136/jnnp-2017-316946

Gazdag, G., & Ungvari, G. S. (2019). Electroconvulsive therapy: 80 years old and still going strong. *World Journal of Psychiatry*, *9*(1), 1–6. https://doi.org/10.5498/wjp.v9.i1.1

Gearon, J. S., Bellack, A. S., Rachbeisel, J., & Dixon, L. (2001). Drug-use behavior and correlates in people with schizophrenia. *Addictive Behaviors*, *26*(1), 51–61. https://doi.org/10.1016/S0306-4603(00)00084-8

Gibbs, P. L. (2007). The primacy of psychoanalytic intervention in recovery from the psychoses and schizophrenias. *The Journal of the American Academy of Psychoanalysis and Dynamic Psychiatry*, *35*(2), 287–312.

Gil, A., Gama, C. S., de Jesus, D. R., Lobato, M. I., Zimmer, M., & Belmonte-de-Abreu, P. (2009). The association of child abuse and neglect with adult disability in schizophrenia and the prominent role of physical neglect. *Child Abuse & Neglect*, *33*(9), 618–624. https://doi.org/10.1016/j.chiabu.2009.02.006

Gilmore, J. H. (2010). Understanding what causes schizophrenia: A developmental perspective. *The American Journal of Psychiatry*, *167*(1), 8–10. https://doi.org/10.1176/appi.ajp.2009.09111588

Gilmour, G., Dix, S., Fellini, L., Gastambide, F., Plath, N., Steckler, T., Talpos, J., & Tricklebank, M. (2012). NMDA receptors, cognition and schizophrenia – testing the validity of the NMDA receptor hypofunction hypothesis. *Neuropharmacology*, *62*(3), 1401–1412. https://doi.org/10.1016/j.neuropharm.2011.03.015

Giovachinni, P., & Boyer, B. L. (1980). *Psychoanalytic Treatment of Schizophrenic Borderline and Characterological Disorders* (Enlarged 2nd Edition). Jason Aronson, Inc.

Girdler, S. J., Confino, J. E., & Woesner, M. E. (2019). Exercise as a Treatment for Schizophrenia: A Review. *Psychopharmacology Bulletin*, *49*(1), 56–69.

Gold, C. (2015). Dose and effect in CBT for schizophrenia. *The British Journal of Psychiatry*, *207*(3), 269–273. https://doi.org/10.1192/bjp.207.3.269

González de Chávez, M. (2009). Treatment of psychoses before the twentieth century. In Y. O. Alanen, M. González de Chávez, A.-L. S. Silver, & B. Martindale (Eds.), *Psychotherapeutic approaches to schizophrenic psychoses: Past, present and future.* (2009-10328-002; pp. 10–22). Routledge/Taylor & Francis Group.

Gonzalez-Flores, B. L. (2020). *Impact of independent exercise on recovery, well-being, and motivation among individuals with schizophrenia* (2020-28121-043; Issues 4-B). ProQuest Information & Learning.

Gottdiener, W. H. (2006). Individual psychodynamic psychotherapy of schizophrenia: Empirical evidence for the practicing clinician. *Psychoanalytic Psychology*, *23*(3), 583–589. https://doi.org/10.1037/0736-9735.23.3.583

Gray, L., Scarr, E., & Dean, B. (2006). Serotonin 1a receptor and associated G-protein activation schizophrenia and bipolar disorder. *Psychiatry Research*, *143*(2), 111–120. https://doi.org/10.1016/j.psychres.2005.09.010

Green, M. F., Horan, W. P., & Lee, J. (2019). Nonsocial and social cognition in schizophrenia: Current evidence and future directions. *World Psychiatry*, *18*(2), 146–161. https://doi.org/10.1002/wps.20624

Grignon, S., & Trottier, M. (2005). Capgras Syndrome in the Modern Era: Self Misidentification on an ID Picture. *The Canadian Journal of Psychiatry / La Revue Canadienne de Psychiatrie*, *50*(1), 74–75.

Grotstein, J. S. (2001). A rationale for the psychoanalytically informed psychotherapy of schizophrenia and other psychoses: Towards the concept of "rehabilitative psychoanalysis." *A Language for Psychosis: Psychoanalysis of Psychotic States.*, 9–26.

Grotstein, J. S. (2003). Towards the concept of "rehabilitative psychoanalytic psychotherapy" in the treatment of schizophrenia. *Preventive Strategies for Schizophrenic Disorders: Basic Principles, Opportunities and Limits.*, 350–365.

Gründer, G., & Cumming, P. (2016). The dopamine hypothesis of schizophrenia: Current status. In T. Abel & T. Nickl-Jockschat (Eds.), *The neurobiology of schizophrenia.* (2016-43112-007; pp. 109–124). Elsevier Academic Press. https://doi.org/10.1016/B978-0-12-801829-3.00015-X

Gur, R. E., Loughead, J., Kohler, C. G., Elliott, M. A., Lesko, K., Ruparel, K., Wolf, D. H., Bilker, W. B., & Gur, R. C. (2007). Limbic activation associated with misidentification of fearful faces and flat affect in schizophrenia. *Archives of General Psychiatry*, *64*(12), 1356–1366. https://doi.org/10.1001/archpsyc.64.12.1356

Hadar, R., Bikovski, L., Soto-Montenegro, M. L., Schimke, J., Maier, P., Ewing, S., Voget, M., Wieske, F., Götz, T., Desco, M., Hamani, C., Pascau, J., Weiner, I., & Winter, C. (2018). Early neuromodulation prevents the development of brain and behavioral abnormalities in a rodent model of schizophrenia. *Molecular Psychiatry*, *23*(4), 943–951. https://doi.org/10.1038/mp.2017.52

Hagiwara, H., Fujita, Y., Ishima, T., Kunitachi, S., Shirayama, Y., Iyo, M., & Hashimoto, K. (2008). Phencyclidine-induced cognitive deficits in mice are improved by subsequent subchronic administration of the antipsychotic drug perospirone: Role of serotonin 5-HT-sub(1A) receptors. *European Neuropsychopharmacology*, *18*(6), 448–454. https://doi.org/10.1016/j.euroneuro.2007.11.005

Hashimoto, T., Bazmi, H. H., Mirnics, K., Wu, Q., Sampson, A. R., & Lewis, D. A. (2008). Conserved regional patterns of GABA-related transcript expression in the neocortex of subjects with schizophrenia. *American Journal of Psychiatry*, *165*(4), 479–489. https://doi.org/10.1176/appi.ajp.2007.07081223

Healy, D. (2006). Neuroleptics and mortality: A 50-year cycle: Invited commentary on... schizophrenia, neuroleptic medication and mortality. *British Journal of Psychiatry*, *188*(2), 128. https://doi.org/10.1192/bjp.bp.105.018911

Hendrick, I. (1928). Encephalitis lethargica and the interpretation of mental disease. *American Journal of Psychiatry*, *7*, 989–1014.

Henssler, J., Brandt, L., Müller, M., Liu, S., Montag, C., Sterzer, P., & Heinz, A. (2020). Migration and schizophrenia: Meta-analysis and explanatory framework. *European Archives of Psychiatry and Clinical Neuroscience*, *270*(3), 325–335. https://doi.org/10.1007/s00406-019-01028-7

Hoeffding, L. K., Rosengren, A., Thygesen, J. H., Schmock, H., Werge, T., & Hansen, T. (2017). Evaluation of shared genetic susceptibility loci between autoimmune diseases and schizophrenia based on genome-wide association studies. *Nordic Journal of Psychiatry*, *71*(1), 20–25. https://doi.org/10.1080/08039488.2016.1198420

Hong, J., & Bang, M. (2020). Anti-inflammatory Strategies for Schizophrenia: A Review of Evidence for Therapeutic Applications and Drug Repurposing. *Clinical Psychopharmacology and Neuroscience*, *18*(1), 10–24. https://doi.org/10.9758/cpn.2020.18.1.10

Høyersten, J. G. (1996). [Possessed! Some historical, psychiatric and curent moments of demonic possession]. *Tidsskrift for Den Norske Laegeforening: Tidsskrift for Praktisk Medicin, Ny Raekke*, *116*(30), 3602–3606.

Hua, M., Peng, Y., Zhou, Y., Qin, W., Yu, C., & Liang, M. (2020). Disrupted pathways from limbic areas to thalamus in schizophrenia highlighted by whole-brain resting-state effective connectivity analysis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *99*, 109837. https://doi.org/10.1016/j.pnpbp.2019.109837

İpçi, K., Yildiz, M., İncedere, A., Kiras, F., Esen, D., & Gürcan, M. B. (2020). Subjective recovery in patients with schizophrenia and related factors. *Community Mental Health Journal*. https://doi.org/10.1007/s10597-020-00616-5

Janssen, I., Krabbendam, L., Bak, M., Hanssen, M., Vollebergh, W., de Graaf, R., & van Os, J. (2004). Childhood abuse as a risk factor for psychotic experiences. *Acta Psychiatrica Scandinavica*, *109*(1), 38–45. https://doi.org/10.1046/j.0001-690X.2003.00217.x

Jauhar, S., McKenna, P. J., Radua, J., Fung, E., Salvador, R., & Laws, K. R. (2014). Cognitive-behavioural therapy for the symptoms of schizophrenia: Systematic review and meta-analysis with examination of potential bias. *The British Journal of Psychiatry*, *204*(1), 20–29. https://doi.org/10.1192/bjp.bp.112.116285

Jentsch, J. D., & Roth, R. H. (1999). The neuropsychopharmacology of phencyclidine: From NMDA receptor hypofunction to the dopamine hypothesis of schizophrenia. *Neuropsychopharmacology*, *20*(3), 201–225. https://doi.org/10.1016/S0893-133X(98)00060-8

Jia, J., Shen, J., Liu, F.-H., Wong, H. K., Yang, X.-J., Wu, Q.-J., Zhang, H., Wang, H.-N., Tan, Q.-R., & Zhang, Z.-J. (2019). Effectiveness of electroacupuncture and electroconvulsive therapy as additional treatment in hospitalized patients with schizophrenia: A retrospective controlled study. *Frontiers in Psychology*, *10*. https://doi.org/10.3389/fpsyg.2019.02306

Joukamaa, M., Heliövaara, M., Knekt, P., Aromaa, A., Raitasalo, R., & Lehtinen, V. (2006). Schizophrenia, neuroleptic medication and mortality. *British Journal of Psychiatry*, *188*(2), 122–127. https://doi.org/10.1192/bjp.188.2.122

Joyal, C. C., Hallé, P., Lapierre, D., & Hodgins, S. (2003). Drug abuse and/or dependence and better neuropsychological performance in patients with schizophrenia. *Schizophrenia Research*, *63*(3), 297–299. https://doi.org/10.1016/S0920-9964(02)00387-0

Juckel, G., & Hoffmann, K. (2018). [The Indian Ayurveda medicine-a meaningful supplement to psychiatric treatment?]. *Der Nervenarzt*, *89*(9), 999–1008. https://doi.org/10.1007/s00115-018-0538-9

Jung, C. G. (1925). The content of the psychoses. In J. S. Van Teslaar (Ed.), *An outline of psychoanalysis.* (2006-21557-012; pp. 255–271). Modern Library. https://doi.org/10.1037/11350-012

Kane, J. M., & Leucht, S. (2008). Unanswered questions in schizophrenia clinical trials. *Schizophrenia Bulletin*, *34*(2), 302–309. https://doi.org/10.1093/schbul/sbm143

Kapelski, P., Hauser, J., Dmitrzak-Weglarz, M., Skibinska, M., Slopien, A., Kaczmarkiewicz-Fass, M., Rajewska, A., Gattner, K., & Czerski, P. M. (2006). Brak asocjacji pomiedzy polimorfizmem insercyjno-delecyjnym promotorowego odcinka genu transportera serotoniny a schizofrenia. *Psychiatria Polska*, *40*(5), 925–935.

Kapsambelis, V. (2019). Psychoanalytic approaches to psychotic disorders in a public mental health system. *British Journal of Psychotherapy*, *35*(4), 577–585. https://doi.org/10.1111/bjp.12482

Kelly, D. L., Rowland, L. M., Patchan, K. M., Sullivan, K., Earl, A., Raley, H., Liu, F., Feldman, S., & McMahon, R. P. (2016). Schizophrenia clinical symptom differences in women vs men with and without a history of childhood physical abuse. *Child and Adolescent Psychiatry and Mental Health*, *10*. https://doi.org/10.1186/s13034-016-0092-9

Kesey, K. (1963). *One Flew Over the Cuckoo's Nest*. Berkley.

Khandaker, G. M., Zimbron, J., Dalman, C., Lewis, G., & Jones, P. B. (2012). Childhood infection and adult schizophrenia: A meta-analysis of population-based studies. *Schizophrenia Research*, *139*(1–3), 161–168. https://doi.org/10.1016/j.schres.2012.05.023

Kim, H., Kim, D., & Kim, S. H. (2018). Association of types of delusions and hallucinations with childhood abuse and neglect among inpatients with schizophrenia in South Korea: A preliminary study. *Psychosis: Psychological, Social and Integrative Approaches*, *10*(3), 208–212. https://doi.org/10.1080/17522439.2018.1472627

Kline, J., Becker, J., & Giese, C. (1992). Psychodynamic interventions revisited: Options for the treatment of schizophrenia. *Psychotherapy: Theory, Research, Practice, Training*, *29*(3), 366–377. https://doi.org/10.1037/h0088538

Knight, J. G. (1982). Dopamine-receptor-stimulating autoantibodies: A possible cause of schizophrenia. *Lancet (London, England)*, *2*(8307), 1073–1076. https://doi.org/10.1016/s0140-6736(82)90007-1

Knight, J. G., Menkes, D. B., Highton, J., & Adams, D. D. (2007). Rationale for a trial of immunosuppressive therapy in acute schizophrenia. *Molecular Psychiatry*, *12*(5), 424–431.

Koch, E., Rosenthal, B., Lundquist, A., Chen, C.-H., & Kauppi, K. (2020). Interactome overlap between schizophrenia and cognition. *Schizophrenia Research*, S0920996420303467. https://doi.org/10.1016/j.schres.2020.06.002

Kohler, C. G., Loughead, J., Ruparel, K., Indersmitten, T., Barrett, F. S., Gur, R. E., & Gur, R. C. (2008). Brain activation during eye gaze discrimination in stable schizophrenia. *Schizophrenia Research*, *99*(1), 286–293. https://doi.org/10.1016/j.schres.2007.09.038

Kortegaard, H. M. (1993). Music therapy in the psychodynamic treatment of schizophrenia. *Music Therapy in Health and Education.*, 55–65.

Kozloff, N., Mulsant, B. H., Stergiopoulos, V., & Voineskos, A. N. (2020). The COVID-19 Global Pandemic: Implications for People with Schizophrenia and Related Disorders. *Schizophrenia Bulletin*. https://doi.org/10.1093/schbul/sbaa051

Krogmann, A., Peters, L., von Hardenberg, L., Bödeker, K., Nöhles, V. B., & Correll, C. U. (2019). Keeping up with the therapeutic advances in schizophrenia: A review of novel and emerging pharmacological entities. *CNS Spectrums*, *24*(S1), 38–69. https://doi.org/10.1017/S109285291900124X

Kroll, J. L. (2007). New directions in the conceptualization of psychotic disorders. *Current Opinion in Psychiatry*, *20*(6), 573–577.

Kumar, V., Vajawat, B., & Rao, N. P. (2020). Frontal gaba in schizophrenia: A meta-analysis of 1h-mrs studies. *The World Journal of Biological Psychiatry*. https://doi.org/10.1080/15622975.2020.1731925

Lamster, F., Kiener, J., Wagner, K., Rief, W., Görge, S. C., Iwaniuk, S., Leube, D., Falkenberg, I., Kluge, I., Kircher, T., & Mehl, S. (2018). Ist Wahn indirekt veränderbar? Ein stimmungsverbesserndes Konzept der kognitive Verhaltenstherapie für die stationäre Standardversorgung von Patienten mit schizophrenen Störungen = Are delusions indirectly alterable? A mood-stabilizing CBT-p concept for inpatients with schizophrenia. *Verhaltenstherapie*, *28*(3), 138–146. https://doi.org/10.1159/000486966

Laskemoen, J. F., Büchmann, C., Barrett, E. A., Collier-Høegh, M., Haatveit, B., Vedal, T. J., Ueland, T., Melle, I., Aas, M., & Simonsen, C. (2020). Do sleep disturbances contribute to cognitive impairments in schizophrenia spectrum and bipolar disorders? *European Archives of Psychiatry and Clinical Neuroscience*, *270*(6), 749–759. https://doi.org/10.1007/s00406-019-01075-0

Laursen, T. M. (2019). Causes of premature mortality in schizophrenia: A review of literature published in 2018. *Current Opinion in Psychiatry*, *32*(5), 388–393. https://doi.org/10.1097/YCO.0000000000000530

Laursen, T. M., Munk-Olsena, T., & Vestergaardb, M. (2012). Life expectancy and cardiovascular mortality in persons with schizophrenia. *Current Opinion in Psychiatry*, *25*(2), 83–88. https://doi.org/10.1097/YCO.0b013e32835035ca

Lawrence, R., Bradshaw, T., & Mairs, H. (2006). Group cognitive behavioural therapy for schizophrenia: A systematic review of the literature. *Journal of Psychiatric and Mental Health Nursing*, *13*(6), 673–681. https://doi.org/10.1111/j.1365-2850.2006.01014.x

Leão, T. S., Sundquist, J., Frank, G., Johansson, L.-M., Johansson, S.-E., & Sundquist, K. (2006). Incidence of schizophrenia or other psychoses in first-and second-generation immigrants: A national cohort study. *Journal of Nervous and Mental Disease*, *194*(1), 27–33. https://doi.org/10.1097/01.nmd.0000195312.81334.81

Leonhardt, B. L., Hamm, J. A., Belanger, E. A., & Lysaker, P. H. (2015). Childhood sexual abuse moderates the relationship of self-reflectivity with increased emotional distress in schizophrenia. *Psychosis: Psychological, Social and Integrative Approaches*, *7*(3), 195–205. https://doi.org/10.1080/17522439.2014.968858

Lester, D. (2007). Suicide mortality in schizophrenics. *Suicide in Schizophrenia.*, 19–29.

Leucht, S., Burkard, T., Henderson, J., Maj, M., & Sartorius, N. (2007). Physical illness and schizophrenia: A review of the literature. *Acta Psychiatrica Scandinavica*, *116*(5), 317–333. https://doi.org/10.1111/j.1600-0447.2007.01095.x

Lewis, S., & Lieberman, J. (2008). CATIE and CutLASS: Can we handle the truth? *British Journal of Psychiatry*, *192*(3), 161–163. https://doi.org/10.1192/bjp.bp.107.037218

Lieberman, J. A., Stroup, T. S., McEvoy, J. P., Swartz, M. S., Rosenheck, R. A., Perkins, D. O., Keefe, R. S. E., Davis, S. M., Davis, C. E., Lebowitz, B. D., Severe, J., & Hsiao, john K. (2005). Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia. *New England Journal of Medicine*, *353*(12), 1209–1223. https://doi.org/10.1056/NEJMoa051688

López-Muñoz, F., Alamo, C., Cuenca, E., Shen, W. W., Clervoy, P., & Rubio, G. (2005). History of the discovery and clinical introduction of chlorpromazine. *Annals of Clinical Psychiatry: Official Journal of the American Academy of Clinical Psychiatrists*, *17*(3), 113–135. https://doi.org/10.1080/10401230591002002

Lorenzo, C. V., Baca-Garcia, E., Diaz-Hernandez, M., Botillo-Martin, C., Perez-Rodriguez, M. M., Fernandez-Ramos, C., Saiz-Gonzalez, M. D., Quintero-Gutierrez, F. J., Saiz-Ruiz, J., Piqueras, J. F., de Rivera, J. L. G., & de Leon, J. (2006). Association between the T102C polymorphism of the serotonin-2A receptor gene and schizophrenia. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *30*(6), 1136–1138. https://doi.org/10.1016/j.pnpbp.2006.04.027

Lublin, H., & Eberhard, J. (2008). Content versus delivery: Challenges and options in the treatment of schizophrenia. *European Neuropsychopharmacology*, *18*(3), v–vi. https://doi.org/10.1016/j.euroneuro.2008.04.001

Lucas, R. (2003). The relationship between psychoanalysis and schizophrenia. *International Journal of Psychoanalysis*, *84*(1), 3–9. https://doi.org/10.1516/00207570360509439

Lysaker, P. H., Beattie, N. L., Strasburger, A. M., & Davis, L. W. (2005). Reported history of child sexual abuse in schizophrenia: Associations with heightened symptom levels and poorer participation over four months in vocational rehabilitation. *Journal of Nervous and Mental Disease*, *193*(12), 790–795. https://doi.org/10.1097/01.nmd.0000188970.11916.76

Lysaker, P. H., Meyer, P. S., Evans, J. D., Clements, C. A., & Marks, K. A. (2001). Childhood Sexual Trauma and Psychosocial Functioning in Adults with Schizophrenia. *Psychiatric Services*, *52*(11), 1485–1488. https://doi.org/10.1176/appi.ps.52.11.1485

Lysaker, P. H., Nees, M. A., Lancaster, R. S., & Davis, L. W. (2004). Vocational function among persons with schizophrenia with and without history of childhood sexual trauma. *Journal of Traumatic Stress*, *17*(5), 435–438. https://doi.org/10.1023/B:JOTS.0000048957.70768.b9

Marneros, A. (2007). Do schizoaffective disorders exist at all? *Acta Psychiatrica Scandinavica*, *115*(2), 162. https://doi.org/10.1111/j.1600-0447.2006.00945.x

Masciotra, L., Landreau, F., Conesa, H. A., & Erausquin, G. A. de. (2005). Pathophysiology of Schizophrenia: A New Look at the Role of Dopamine. *Trends in Schizophrenia Research.*, 27–44.

Maurel, M., Belzeaux, R., Adida, M., Fakra, E., Cermolacce, M., Da Fonseca, D., & Azorin, J.-M. (2011). Schizophrénie, cognition et psycho-éducation = Schizophrenia, cognition and psychoeducation. *L'Encéphale: Revue de Psychiatrie Clinique Biologique et Thérapeutique*, *37*(Suppl 2), S151–S154. https://doi.org/10.1016/S0013-7006(11)70043-4

May, P. (1968). *Treatment of schizophrenia; A comparative study of five treatment methods* (First Edition edition). Science House.

McGrath, J., Brown, A., & St Clair, D. (2011). Prevention and Schizophrenia—The Role of Dietary Factors. *Schizophrenia Bulletin*, *37*(2), 272–283. https://doi.org/10.1093/schbul/sbq121

McGrath, J. J. (2006). Variations in the incidence of schizophrenia: Data versus dogma. *Schizophrenia Bulletin*, *32*(1), 195–197. https://doi.org/10.1093/schbul/sbi052

Meyer, U., Murray, P. J., Urwyler, A., Yee, B. K., Schedlowski, M., & Feldon, J. (2008). Adult behavioral and pharmacological dysfunctions following disruption of the fetal brain balance between pro-inflammatory and IL-10-mediated anti-inflammatory signaling. *Molecular Psychiatry*, *13*(2), 208–221. https://doi.org/10.1038/sj.mp.4002042

Meyer, Urs, Feldon, J., Schedlowski, M., & Yee, B. K. (2006). Immunological stress at the maternal-foetal interface: A link between neurodevelopment and adult psychopathology. *Brain, Behavior, and Immunity*, *20*(4), 378–388. https://doi.org/10.1016/j.bbi.2005.11.003

Meyer, Urs, Nyffeler, M., Schwendener, S., Knuesel, I., Yee, B. K., & Feldon, J. (2008). Relative prenatal and postnatal maternal contributions to schizophrenia-related neurochemical dysfunction after in utero immune challenge. *Neuropsychopharmacology*, *33*(2), 441–456. https://doi.org/10.1038/sj.npp.1301413

Miller, B. J., Buckley, P., Seabolt, W., Mellor, A., & Kirkpatrick, B. (2011). Meta-Analysis of Cytokine Alterations in Schizophrenia: Clinical Status and Antipsychotic Effects. *Biological Psychiatry*, *70*(7), 663–671. https://doi.org/10.1016/j.biopsych.2011.04.013

Miller, P., Lawrie, S. M., Hodges, A., Clafferty, R., Cosway, R., & Johnstone, E. C. (2001). Genetic liability, illicit drug use, life stress and psychotic symptoms: Preliminary findings from the Edinburgh study of people at high risk for schizophrenia. *Social Psychiatry and Psychiatric Epidemiology*, *36*(7), 338–342. https://doi.org/10.1007/s001270170038

Mishra, A., Mishra, A. K., & Jha, S. (2018). Effect of traditional medicine brahmi vati and bacoside A-rich fraction of Bacopa monnieri on acute pentylenetetrzole-induced seizures, amphetamine-induced model of schizophrenia, and scopolamine-induced memory loss in laboratory animals. *Epilepsy & Behavior: E&B*, *80*, 144–151. https://doi.org/10.1016/j.yebeh.2017.12.040

Mitsadali, I., Grayson, B., Idris, N. F., Watson, L., Burgess, M., & Neill, J. (2020). Aerobic exercise improves memory and prevents cognitive deficits of relevance to schizophrenia in an animal model. *Journal of Psychopharmacology*, *34*(7), 695–708. https://doi.org/10.1177/0269881120922963

Mittal, V. A., Saczawa, M. E., Walker, E., Willhite, R., & Walder, D. (2008). Prenatal exposure to viral infection and conversion among adolescents at high-risk for psychotic disorders. *Schizophrenia Research*, *99*(1), 375–376. https://doi.org/10.1016/j.schres.2007.11.037

Møllerhøj, J., Os Stølan, L., Erdner, A., Hedberg, B., Stahl, K., Riise, J., Jedenius, E., & Rise, M. B. (2019). 'i live, I don't work, but I live a very normal life'—A qualitative interview study of scandinavian user experiences of schizophrenia, antipsychotic medication, and personal recovery processes. *Perspectives in Psychiatric Care*. https://doi.org/10.1111/ppc.12444

Moran, E. K., Gold, J. M., Carter, C. S., MacDonald, A. W., Ragland, J. D., Silverstein, S. M., Luck, S. J., & Barch, D. M. (2020). Both unmedicated and medicated individuals with schizophrenia show impairments across a wide array of cognitive and reinforcement learning tasks. *Psychological Medicine*. https://doi.org/10.1017/S003329172000286X

Moreno, J. L., Kurita, M., Holloway, T., López, J., Cadagan, R., Martínez-Sobrido, L., García-Sastre, A., & González-Maeso, J. (2011). Maternal influenza viral infection causes schizophrenia- like alterations of 5-HT2A and mGlu$_2$ receptors in the adult offspring. *The Journal of Neuroscience*, *31*(5), 1863–1872. https://doi.org/10.1523/JNEUROSCI.4230-10.2011

Mueser, K. T., & Berenbaum, H. (1990). Psychodynamic treatment of schizophrenia: Is there a future? *Psychological Medicine*, *20*(2), 253–262.

Mullen, P. E. (2005). Child sexual abuse and schizophrenia: Author's reply. *The British Journal of Psychiatry*, *186*(1), 76–76.

Murray, R. M., Grech, A., Phillips, P., & Johnson, S. (2003). What is the relationship between substance abuse and schizophrenia? In R. M. Murray, P. B. Jones, E. Susser, J. van Os, & M. Cannon (Eds.), *The epidemiology of schizophrenia.* (2003-04863-016; pp. 317–342). Cambridge University Press.

Nelson, C. L. M., Amsbaugh, H. M., Reilly, J. L., Rosen, C., Marvin, R. W., Ragozzino, M. E., Bishop, J. R., Sweeney, J. A., & Hill, S. K. (2018). Beneficial and adverse effects of antipsychotic medication on cognitive flexibility are related to COMT genotype in first episode psychosis. *Schizophrenia Research*, *202*, 212–216. https://doi.org/10.1016/j.schres.2018.06.029

Niebuhr, D. W., Millikan, A. M., Cowan, D. N., Yolken, R., Li, Y., & Weber, N. S. (2008). Selected infectious agents and risk of schizophrenia among U.S. Military personnel. *American Journal of Psychiatry*, *165*(1), 99–106. https://doi.org/10.1176/appi.ajp.2007.06081254

Nightingale, L. C., & McQueeney, D. A. (1996). Group therapy for schizophrenia: Combining and expanding the psychoeducational model with supportive psychotherapy. *International Journal of Group Psychotherapy*, *46*(4), 517–533.

Nixon, N. L., & Doody, G. A. (2005). Official psychiatric morbidity and the incidence of schizophrenia 1881-1994. *Psychological Medicine*, *35*(8), 1145–1153. https://doi.org/10.1017/S0033291705004939

Ohara, K. (2007). The n-3 polyunsaturated fatty acid/dopamine hypothesis of schizophrenia. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *31*(2), 469–474. https://doi.org/10.1016/j.pnpbp.2006.11.013

Ortiz-Medina, M. B., Perea, M., Torales, J., Ventriglio, A., Vitrani, G., Aguilar, L., & Roncero, C. (2018). Cannabis consumption and psychosis or schizophrenia development. *International Journal of Social Psychiatry*, *64*(7), 690–704. https://doi.org/10.1177/0020764018801690

Ottet, M.-C., Schaer, M., Cammoun, L., Schneider, M., Debbané, M., Thiran, J.-P., & Eliez, S. (2013). Reduced fronto-temporal and limbic connectivity in the 22q112 deletion syndrome: Vulnerability markers for developing schizophrenia? *PLoS ONE*, *8*(3). https://doi.org/10.1371/journal.pone.0058429

Pandurangi, A. K., & Buckley, P. F. (2020). Inflammation, Antipsychotic Drugs, and Evidence for Effectiveness of Anti-inflammatory Agents in Schizophrenia. In G. M. Khandaker, U. Meyer, & P. B. Jones (Eds.), *Neuroinflammation and Schizophrenia* (pp. 227–244). Springer International Publishing. https://doi.org/10.1007/7854_2019_91

Pang, N., Thrichelvam, N., & Naing, K. O. (2017). Olanzapine-induced Pancytopenia: A Rare but Worrying Complication. *East Asian Archives of Psychiatry: Official Journal of the Hong Kong College of Psychiatrists = Dong Ya Jing Shen Ke Xue Zhi: Xianggang Jing Shen Ke Yi Xue Yuan Qi Kan*, *27*(1), 35–37.

Peltzer, K. (1999). Faith Healing for Mental and Social Disorders in the Northern Province (South Africa). *Journal of Religion in Africa*, *29*(3), 387–402.

Potvin, S., Stip, E., Sepehry, A. A., Gendron, A., Bah, R., & Kouassi, E. (2008). Inflammatory cytokine alterations in schizophrenia: A systematic quantitative review. *Biological Psychiatry*, *63*(8), 801–808.

Poulet, E., Brunelin, J., Kallel, L., D'Amato, T., & Saoud, M. (2008). Maintenance treatment with transcranial magnetic stimulation in a patient with late-onset schizophrenia. *American Journal of Psychiatry*, *165*(4), 537–538. https://doi.org/10.1176/appi.ajp.2007.07060868

Prasad, K. M. R., Shirts, B. H., Yolken, R. H., Keshavan, M. S., & Nimgaonkar, V. L. (2007a). Brain morphological changes associated with exposure to HSV1 in first-episode schizophrenia. *Molecular Psychiatry*, *12*(1), 105–113. https://doi.org/10.1038/sj.mp.4001915

Prasad, K. M. R., Shirts, B. H., Yolken, R. H., Keshavan, M. S., & Nimgaonkar, V. L. (2007b). HSV1 exposure affects prefrontal cortical structure in schizophrenia patients. *Molecular Psychiatry*, *12*(1), 1. https://doi.org/10.1038/sj.mp.4001942

Pratt, L. A. (2012). Characteristics of adults with serious mental illness in the United States household population in 2007. *Psychiatric Services*, *63*(10), 1042–1046. https://doi.org/10.1176/appi.ps.201100442

Rado, J. T., & Hernandez, E. I. (2014). Therapeutic neuromodulation for treatment of schizophrenia. In P. G. Janicak, S. R. Marder, R. Tandon, & M. Goldman (Eds.), *Schizophrenia: Recent advances in diagnosis and treatment.* (2014-26994-008; pp. 139–160). Springer Science + Business Media.

Rakitzi, S., Georgila, P., & Becker-Woitag, A. P. (2020). The recovery process for individuals with schizophrenia in the context of evidence-based psychotherapy and rehabilitation: A systematic review. *European Psychologist*. https://doi.org/10.1027/1016-9040/a000400

Ran, M.-S., Chen, E. Y.-H., Conwell, Y., Lai-Wan Chan, C., Yip, P. S. F., Xiang, M.-Z., & Caine, E. D. (2007). Mortality in people with schizophrenia in rural China: 10-year cohort study. *British Journal of Psychiatry*, *190*(3), 237–242. https://doi.org/10.1192/bjp.bp.106.025155

Rashno, M. M., Fallahi, S., Arab-Mazar, Z., & Dana, H. (2019). Seromolecular assess of Toxoplasma gondii infection in pregnant women and neonatal umbilical cord blood. *EXCLI Journal*, *18*, 1–7.

Rathbone, J., Zhang, L., Zhang, M., Xia, J., Liu, X., Yang, Y., & Adams, C. E. (2007). Chinese herbal medicine for schizophrenia: Cochrane systematic review of randomised trials. *The British Journal of Psychiatry*, *190*, 379–384. https://doi.org/10.1192/bjp.bp.106.026880

Read, J., van Os, J., Morrison, A. P., & Ross, C. A. (2005). Childhood trauma, psychosis and schizophrenia: A literature review with theoretical and clinical implications. *Acta Psychiatrica Scandinavica*, *112*(5), 330–350. https://doi.org/10.1111/j.1600-0447.2005.00634.x

Read, John, Agar, K., Argyle, N., & Aderhold, V. (2003). Sexual and physical abuse during childhood and adulthood as predictors of hallucinations, delusions and thought disorder. *Psychology and Psychotherapy: Theory, Research and Practice*, *76*(1), 1–22. https://doi.org/10.1348/14760830260569210

Richard, M. D., & Brahm, N. C. (2012). Schizophrenia and the immune system: Pathophysiology, prevention, and treatment. *American Journal of Health-System Pharmacy: AJHP: Official Journal of the American Society of Health-System Pharmacists*, *69*(9), 757–766. https://doi.org/10.2146/ajhp110271

Robinson, D. S. (2008). Mortality risks and antipsychotics. *Primary Psychiatry*, *15*(4), 21–23.

Rokita, K. I., Dauvermann, M. R., Mothersill, D., Holleran, L., Holland, J., Costello, L., Cullen, C., Kane, R., McKernan, D., Morris, D. W., Kelly, J., Gill, M., Corvin, A., Hallahan, B., McDonald, C., & Donohoe, G. (2020). Childhood trauma, parental bonding, and social cognition in patients with schizophrenia and healthy adults. *Journal of Clinical Psychology*. https://doi.org/10.1002/jclp.23023

Roser, P. (2019). Cannabis und Schizophrenie—Risikofaktoren, diagnostische Einordnung und Auswirkungen auf Verlauf und Prognose = Cannabis and schizophrenia—Risk factors, diagnostic classification and effects on course and outcome. *Forensische Psychiatrie, Psychologie, Kriminologie*, *13*(3), 225–232. https://doi.org/10.1007/s11757-019-00543-6

Ross, C. (2014). Dissociation in classical texts on schizophrenia. *Psychosis: Psychological, Social and Integrative Approaches*, *6*(4), 342–354. https://doi.org/10.1080/17522439.2013.806570

Ross, C. A. (2006). Dissociation and psychosis: The need for integration of theory and practice. *Evolving Psychosis.*, 238–254.

Rossello, J.-J., Gaillard, G., & Neuilly, M.-T. (2013). Une institution en quête de limites. Le mythe de Tom Sawyer: Un objet transitionnel collectif. = An institution seeking limits. The myth of Tom Sawyer : A collective transitional object. *Revue de Psychothérapie Psychanalytique de Groupe*, *60*, 141–152. https://doi.org/10.3917/rppg.060.0141

Ryan, J. E., Veliz, P., McCabe, S. E., Stoddard, S. A., & Boyd, C. J. (2020). Association of early onset of cannabis, cigarette, other drug use and schizophrenia or psychosis. *Schizophrenia Research*, *215*, 482–484. https://doi.org/10.1016/j.schres.2019.10.002

Sabe, M., Kaiser, S., & Sentissi, O. (2020). Physical exercise for negative symptoms of schizophrenia: Systematic review of randomized controlled trials and meta-analysis. *General Hospital Psychiatry*, *62*, 13–20. https://doi.org/10.1016/j.genhosppsych.2019.11.002

Saha, S., Chant, D. C., Welham, J. L., & McGrath, J. J. (2006). The incidence and prevalence of schizophrenia varies with latitude. *Acta Psychiatrica Scandinavica*, *114*(1), 36–39. https://doi.org/10.1111/j.1600-0447.2005.00742.x

Saha, S., Chant, D., & McGrath, J. (2007). A systematic review of mortality in schizophrenia: Is the differential mortality gap worsening over time? *Archives of General Psychiatry*, *64*(10), 1123–1131. https://doi.org/10.1001/archpsyc.64.10.1123

Saha, S., Welham, J., Chant, D., & McGrath, J. (2006). Incidence of schizophrenia does not vary with economic status of the country: Evidence from a systematic review. *Social Psychiatry and Psychiatric Epidemiology*, *41*(5), 338–340. https://doi.org/10.1007/s00127-006-0041-7

Sarter, M., Nelson, C. L., & Bruno, J. P. (2005). Cortical Cholinergic Transmission and Cortical Information Processing in Schizophrenia. *Schizophrenia Bulletin*, *31*(1), 117–138. https://doi.org/10.1093/schbul/sbi006

Schürhoff, F., Laguerre, A., Fisher, H., Etain, B., Méary, A., Soussy, C., Szöke, A., & Leboyer, M. (2009). Self-reported childhood trauma correlates with schizotypal measures in schizophrenia but not bipolar pedigrees. *Psychological Medicine*, *39*(3), 365–370. https://doi.org/10.1017/S0033291708003905

Schwab, S. G., & Wildenauer, D. B. (2008). Research on causes for schizophrenia: Are we close? *Schizophrenia Research*, *102*(1), 29–30. https://doi.org/10.1016/j.schres.2008.04.005

Scull, A. (2005). *Madhouse: A Tragic Tale of Megalomania and Modern Medicine* (1st ed.). Yale University Press.

Searles, H. F. (1986). *Collected Papers on Schizophrenia and Related Subjects* (1 edition). Routledge.

Seeman, P. (2000). Antipsychotic drugs, dopamine D2 receptors, and schizophrenia. *Neurotransmitter Receptors in Actions of Antipsychotic Medications.*, 43–63.

Sepehry, A. A., Potvin, S., Élie, R., & Stip, E. (2007). Selective serotonin reuptake inhibitor (SSRI) add-on therapy for the negative symptoms of schizophrenia: A meta-analysis. *Journal of Clinical Psychiatry*, *68*(4), 604–610.

Setién-Suero, E., Neergaard, K., Ortiz-García de la Foz, V., Suárez-Pinilla, P., Martínez-García, O., Crespo-Facorro, B., & Ayesa-Arriola, R. (2019). Stopping cannabis use benefits outcome in psychosis: Findings from 10-year follow-up study in the PAFIP-cohort. *Acta Psychiatrica Scandinavica*, *140*(4), 349–359. https://doi.org/10.1111/acps.13081

Severance, E. G., Prandovszky, E., Castiglione, J., & Yolken, R. H. (2015). Gastroenterology issues in schizophrenia: Why the gut matters. *Current Psychiatry Reports*, *17*(5), 27. https://doi.org/10.1007/s11920-015-0574-0

Severance, E. G., & Yolken, R. H. (2020). From Infection to the Microbiome: An Evolving Role of Microbes in Schizophrenia. *Current Topics in Behavioral Neurosciences*, *44*, 67–84. https://doi.org/10.1007/7854_2018_84

Severance, E. G., Yolken, R. H., & Eaton, W. W. (2016). Autoimmune diseases, gastrointestinal disorders and the microbiome in schizophrenia: More than a gut feeling. *Schizophrenia Research*, *176*(1), 23–35. https://doi.org/10.1016/j.schres.2014.06.027

Shekunov, J. (2016). Immigration and Risk of Psychiatric Disorders: A Review of Existing Literature. *American Journal of Psychiatry Residents' Journal*, *11*(2), 3–5. https://doi.org/10.1176/appi.ajp-rj.2016.110202

Shimada, T., Ito, S., Makabe, A., Yamanushi, A., Takenaka, A., & Kobayashi, M. (2019). Aerobic exercise and cognitive functioning in schizophrenia: A pilot randomized controlled trial. *Psychiatry Research*, *282*. https://doi.org/10.1016/j.psychres.2019.112638

Shonin, E., Van Gordon, W., & Griffiths, M. D. (2014). Cognitive behavioral therapy (CBT) and Meditation Awareness Training (MAT) for the treatment of co-occurring schizophrenia and pathological gambling: A case study. *International Journal of Mental Health and Addiction*, *12*(2), 181–196. https://doi.org/10.1007/s11469-013-9460-3

Silva, M. A., & Restrepo, D. (2019). Recuperación funcional en la esquizofrenia = Functional recovery in schizophrenia. *Revista Colombiana de Psiquiatría*, *48*(4), 252–260. https://doi.org/10.1016/j.rcp.2017.08.004

Sim, K., Chan, Y. H., Chua, T. H., Mahendran, R., Chong, S. A., & McGorry, P. (2006). Physical comorbidity, insight, quality of life and global functioning in first episode schizophrenia: A 24-month, longitudinal outcome study. *Schizophrenia Research*, *88*(1), 82–89. https://doi.org/10.1016/j.schres.2006.07.004

Sim, K., Chua, T. H., Chan, Y. H., Mahendran, R., & Chong, S. A. (2006). Psychiatric comorbidity in first episode schizophrenia: A 2 year, longitudinal outcome study. *Journal of Psychiatric Research*, *40*(7), 656–663. https://doi.org/10.1016/j.jpsychires.2006.06.008

Simeone, J. C., Ward, A. J., Rotella, P., Collins, J., & Windisch, R. (2015). An evaluation of variation in published estimates of schizophrenia prevalence from 1990-2013: A systematic literature review. *BMC Psychiatry*, *15*(1), 1–14. https://doi.org/10.1186/s12888-015-0578-7

Sommer, I. E., de Witte, L., Begemann, M., & Kahn, R. S. (2012). Nonsteroidal anti-inflammatory drugs in schizophrenia: Ready for practice or a good start? A meta-analysis. *The Journal of Clinical Psychiatry*, *73*(4), 414–419. https://doi.org/10.4088/JCP.10r06823

Spataro, J., Mullen, P. E., Burgess, P. M., Wells, D. L., & Moss, S. A. (2004). Impact of child sexual abuse on mental health: Prospective study in males and females. *The British Journal of Psychiatry*, *184*(5), 416–421. https://doi.org/10.1192/bjp.184.5.416

Staudt, M. D., Herring, E. Z., Gao, K., Miller, J. P., & Sweet, J. A. (2019). Evolution in the Treatment of Psychiatric Disorders: From Psychosurgery to Psychopharmacology to Neuromodulation. *Frontiers in Neuroscience*, *13*. https://doi.org/10.3389/fnins.2019.00108

Steel, C. (2013). *CBT for schizophrenia: Evidence-based interventions and future directions* (C. Steel, Ed.; 2013-04591-000). Wiley Blackwell. https://doi.org/10.1002/9781118330029

Stone, M. H. (1999). The History of the Psychoanalytic Treatment of Schizophrenia. *J. Amer. Acad. Psychoanal.*, 583–601.

Sudak, D. M. (2004). Cognitive-behavioral therapy for schizophrenia. *Journal of Psychiatric Practice*, *10*(5), 331–333. https://doi.org/10.1097/00131746-200409000-00007

Sumiyoshi, T., Park, S., Jayathilake, K., Roy, A., Ertugrul, A., & Meltzer, H. Y. (2007). Effect of buspirone, a serotonin-sub(1A) partial agonist, on cognitive function in schizophrenia: A randomized, double-blind, placebo-controlled study. *Schizophrenia Research*, *95*(1), 158–168. https://doi.org/10.1016/j.schres.2007.06.008

Sutterland, A. L., Kuin, A., Kuiper, B., van Gool, T., Leboyer, M., Fond, G., & de Haan, L. (2019). Driving us mad: The association of Toxoplasma gondii with suicide attempts and traffic accidents—A systematic review and meta-analysis. *Psychological Medicine*, *49*(10), 1608–1623. https://doi.org/10.1017/S0033291719000813

Suvisaari, J. M., Haukka, J. K., Tanskanen, A. J., & Lönnqvist, J. K. (1999). Decline in the incidence of schizophrenia in Finnish cohorts born from 1954 to 1965. *Archives of General Psychiatry*, *56*(8), 733–740. https://doi.org/10.1001/archpsyc.56.8.733

Szumlinski, K. K., & Kippin, T. E. (2008). Homer: A genetic factor in schizophrenia? *Cortical Deficits in Schizophrenia: From Genes to Function.*, 29–72.

Tandon, R., Nasrallah, H. A., & Keshavan, M. S. (2010). Schizophrenia, "Just the Facts" 5. Treatment and prevention Past, present, and future. *Schizophrenia Research*, *122*(1), 1–23. https://doi.org/10.1016/j.schres.2010.05.025

Thomann, P. A., Wolf, R. C., Nolte, H. M., Hirjak, D., Hofer, S., Seidl, U., Depping, M. S., Stieltjes, B., Maier-Hein, K., Sambataro, F., & Wüstenberg, T. (2017). Neuromodulation in response to electroconvulsive therapy in schizophrenia and major depression. *Brain Stimulation*, *10*(3), 637–644. https://doi.org/10.1016/j.brs.2017.01.578

Tidd, C. W. (1937). Increasing reality acceptance by a schizoid personality during analysis. *Bulletin of the Menninger Clinic*, *1*, 176–183.

Tidd, C. W. (1938). A note on the treatment of schizophrenia. *Bulletin of the Menninger Clinic*, *2*, 89–93.

Tochigi, M., Okazaki, Y., Kato, N., & Sasaki, T. (2004). What causes seasonality of birth in schizophrenia? *Neuroscience Research*, *48*(1), 1–11. https://doi.org/10.1016/j.neures.2003.09.002

Torrey, E. F., Bartko, J. J., & Yolken, R. H. (2012). Toxoplasma gondii and Other Risk Factors for Schizophrenia: An Update. *Schizophrenia Bulletin*, *38*(3), 642–647. https://doi.org/10.1093/schbul/sbs043

Trudeau, K. J., Burtner, J., Villapiano, A. J., Jones, M., Butler, S. F., & Joshi, K. (2018). Burden of schizophrenia or psychosis-related symptoms in adults undergoing substance abuse evaluation. *Journal of Nervous and Mental Disease*, *206*(7), 528–536.

Tsapakis, E.-M., Guillin, O., & Murray, R. M. (2003). Does dopamine sensitization underlie the association between schizophrenia and drug abuse? *Current Opinion in Psychiatry*, *16*, S45-s52. https://doi.org/10.1097/00001504-200304002-00008

Turkington, D., Dudley, R., Warman, D. M., & Beck, A. T. (2004). Cognitive-behavioral therapy for schizophrenia: A review. *Journal of Psychiatric Practice*, *10*(1), 5–16. https://doi.org/10.1097/00131746-200401000-00002

Turkington, D., Kingdon, D., & Chadwick, P. (2003). Cognitive-behavioural therapy for schizophrenia: Filling the therapeutic vacuum. *British Journal of Psychiatry*, *183*(2), 98–99. https://doi.org/10.1192/bjp.183.2.98

Valon, P. (2020). Gisela Pankow (1914–1998): Towards a psychoanalytic treatment of the psychoses. *The International Journal of Psychoanalysis*, *101*(1), 169–185. https://doi.org/10.1080/00207578.2020.1716628

Vaucher, J., Keating, B. J., Lasserre, A. M., Gan, W., Lyall, D. M., Ward, J., Smith, D. J., Pell, J. P., Sattar, N., Paré, G., & Holmes, M. V. (2018). Cannabis use and risk of schizophrenia: A Mendelian randomization study. *Molecular Psychiatry*, *23*(5), 1287–1292. https://doi.org/10.1038/mp.2016.252

Vidal, S., & Huguelet, P. (2019). Thérapie cognitive basée sur le concept de rétablissement pour la schizophrénie: Un cas clinique = Recovery Oriented Cognitive Therapy for schizophrenia: A case report. *Journal de Thérapie Comportementale et Cognitive*, *29*(2), 57–66. https://doi.org/10.1016/j.jtcc.2018.11.001

Vogel, M., Meier, J., Grönke, S., Waage, M., Schneider, W., Freyberger, H. J., & Klauer, T. (2011). Differential effects of childhood abuse and neglect: Mediation by posttraumatic distress in neurotic disorder and negative symptoms in schizophrenia? *Psychiatry Research*, *189*(1), 121–127. https://doi.org/10.1016/j.psychres.2011.01.008

Volkan, V. D. (2012). *Psychoanalytic Technique Expanded: A Textbook on Psychoanalytic Treatment*. Pitchstone Publishing.

Volkan, V. D. (1995). *The infantile psychotic self and its fates: Understanding and treating schizophrenics and other difficult patients* (1995-98163-000). Jason Aronson.

Wang, A. W., Avramopoulos, D., Lori, A., Mulle, J., Conneely, K., Powers, A., Duncan, E., Almli, L., Massa, N., McGrath, J., Schwartz, A. C., Goes, F. S., Weng, L., Wang, R., Yolken, R., Ruczinski, I., Gillespie, C. F., Jovanovic, T., Ressler, K., … Pearce, B. D. (2019). Genome-wide association study in two populations to determine genetic variants associated with Toxoplasma gondii infection and relationship to schizophrenia risk. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *92*, 133–147. https://doi.org/10.1016/j.pnpbp.2018.12.019

Wang, L.-Y., Chen, S.-F., Chiang, J.-H., Hsu, C.-Y., & Shen, Y.-C. (2018). Autoimmune diseases are associated with an increased risk of schizophrenia: A nationwide population-based cohort study. *Schizophrenia Research*, *202*, 297–302. https://doi.org/10.1016/j.schres.2018.06.033

Warman, D. M., & Beck, A. T. (2003). Cognitive behavioral therapy for schizophrenia: An overview of treatment. *Cognitive and Behavioral Practice*, *10*(3), 248–254. https://doi.org/10.1016/S1077-7229(03)80037-8

Weininger, B. I. (1938). Psychotherapy during convalescence from psychosis. *Psychiatry: Journal for the Study of Interpersonal Processes*, *2*, 257–264.

Weiser, M., Reichenberg, A., Rabinowitz, J., Kaplan, Z., Caspi, A., Yasvizky, R., Mark, M., Knobler, H. Y., Nahon, D., & Davidson, M. (2003). Self-Reported Drug Abuse in Male Adolescents with Behavioral Disturbances, and Follow-up for Future Schizophrenia. *Biological Psychiatry*, *54*(6), 655–660. https://doi.org/10.1016/S0006-3223(03)00110-0

Whitaker, R. (2002). *Mad in America: Bad Science, Bad Medicine, And the Enduring Mistreatment Of The Mentally Ill* (1St Edition edition). Basic Books.

White, T., Cullen, K., Rohrer, L. M., Karatekin, C., Luciana, M., Schmidt, M., Hongwanishkul, D., Kumra, S., Schulz, S. C., & Lim, K. O. (2008). Limbic structures and networks in children and adolescents with schizophrenia. *Schizophrenia Bulletin*, *34*(1), 18–29. https://doi.org/10.1093/schbul/sbm110

Williams, L. (Lea) M., Das, P., Liddell, B. J., Olivieri, G., Peduto, A. S., David, A. S., Gordon, E., & Harris, A. W. F. (2007). Fronto-limbic and autonomic disjunctions to negative emotion distinguish schizophrenia subtypes. *Psychiatry Research: Neuroimaging*, *155*(1), 29–44. https://doi.org/10.1016/j.pscychresns.2006.12.018

Winterer, G. (2006). Cortical Microcircuits in Schizophrenia—The Dopamine Hypothesis Revisited. *Pharmacopsychiatry*, *39*, S68-s71. https://doi.org/10.1055/s-2006-931498

Włodarczyk, A., Szarmach, J., Cubała, W. J., & Wiglusz, M. S. (2017). Benzodiazepines in combination with antipsychotic drugs for schizophrenia: GABA-ergic targeted therapy. *Psychiatria Danubina*, *29*(Suppl 3), 345–348.

Wortinger, L. A., Engen, K., Barth, C., Lonning, V., Jørgensen, K. N., Andreassen, O. A., Haukvik, U. K., Vaskinn, A., Ueland, T., & Agartz, I. (2020). Obstetric complications and intelligence in patients on the schizophrenia-bipolar spectrum and healthy participants. *Psychological Medicine*, *50*(11), 1914–1922. https://doi.org/10.1017/S0033291719002046

Wotruba, D., Michels, L., Buechler, R., Metzler, S., Theodoridou, A., Gerstenberg, M., Walitza, S., Kollias, S., Rössler, W., & Heekeren, K. (2014). Aberrant Coupling Within and Across the Default Mode, Task-Positive, and Salience Network in Subjects at Risk for Psychosis. *Schizophrenia Bulletin*, *40*(5), 1095–1104. https://doi.org/10.1093/schbul/sbt161

Xiao, J., Prandovszky, E., Kannan, G., Pletnikov, M. V., Dickerson, F., Severance, E. G., & Yolken, R. H. (2018). Toxoplasma gondii: Biological parameters of the connection to schizophrenia. *Schizophrenia Bulletin*, *44*(5), 983–992. https://doi.org/10.1093/schbul/sby082

Xu, J., He, G., Zhu, J., Zhou, X., St Clair, D., Wang, T., Xiang, Y., Zhao, Q., Xing, Q., Liu, Y., Wang, L., Li, Q., He, L., & Zhao, X. (2015). Prenatal nutritional deficiency reprogrammed postnatal gene expression in mammal brains: Implications for schizophrenia. *International Journal of Neuropsychopharmacology*, *18*(4), 1–9. https://doi.org/10.1093/ijnp/pyu054

Xu, L., Qi, X., Zhu, C., & Wan, L. (2018). Activation of IL-8 and its participation in cancer in schizophrenia patients: New evidence for the autoimmune hypothesis of schizophrenia. *Neuropsychiatric Disease and Treatment*, *14*. https://doi.org/10.2147/NDT.S188210

Xu, X. J., & Jiang, G. S. (2015). Niacin-respondent subset of schizophrenia – a therapeutic review. *European Review for Medical and Pharmacological Sciences*, *19*(6), 988–997.

Zandifar, A., & Badrfam, R. (2020). COVID-19: Considering the prevalence of schizophrenia in the coming decades. *Psychiatry Research*, *288*, 112982. https://doi.org/10.1016/j.psychres.2020.112982

Zhenxing, Y., Longkun, L., & Miaoxin, L. (2018). De novo mutations as causes of schizophrenia. *Psychiatry Research*, *270*, 1168–1169. https://doi.org/10.1016/j.psychres.2018.05.037

Zullino, D. F., Manghi, R., Rathelot, T., Khan, R., & Khazaal, Y. (2010). Cannabis causes schizophrenia? So does nicotine. *Addiction Research & Theory*, *18*(6), 601–605. https://doi.org/10.3109/16066359.2010.489999