Indranath Chatterjee *Editor*

Cognizance of Schizophrenia: A Profound Insight into the Psyche

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Preface

Ever wonder what you can ask a person living with schizophrenia? Unfortunately, it is not very clear to answer this query. The consciousness of the mind of schizophrenia patients is complicated. Schizophrenia patients sometimes become very delicate and sensitive. Various thoughts, visions, and voices are being perceived within their brain. Having a long history of the disorder, schizophrenia is still considered a severe mental illness, majorly a chronic psychological disorder. Although controversies are there to consider it a neuro-psychological disorder, neuroscientists, clinicians, and interdisciplinary researchers are thriving to comprehend it completely.

As mentioned, schizophrenia is a complex brain disorder, where various aspects are being investigated for its cognizance. Starting from epigenetics to chemistry and physics to computational approaches, the scope of research on schizophrenia is never-ending. There are several things in this book we are covering to help the readers with profound knowledge of schizophrenia from every possible aspect. This book elaborates on the key concepts of schizophrenia from various aspects such as neurogenetics, neurochemistry, neuropharmacology, neurobiology, psychotherapy, psychiatric treatment, cognitive study, brain dynamics, and computational neuroscience. This book explains each section and chapter with utmost clarity to maintain comprehensiveness for every kind of reader. This book covers various classical as well as recent topics from basic to advanced level knowledge regarding schizophrenia.

This book will indeed outperform most of the available books on the market. The book's contributions regarding its inclusivity of topics, comprehensiveness of language, diversity in knowledge, and focus on the subject will attract all kinds of readers. It can be considered a single comprehensive handy reference book for beginners, including medical students, neuroscientists, researchers, clinicians, and medical practitioners. To mention a few core points to prove its outperformance over any other competitive book, the following can be considered:

1. Written in simple language for understanding across the globe.
2. Topics are easily explained with examples.
3. A smooth flow of content while shifting from primary to advanced topics for better adaptation of readers' minds.
4. A deep study of the topics.
5. Written in a straightforward method for easy comprehensiveness.
6. A single book on schizophrenia comprises various aspects to understand the illness from every direction.
7. Discussion on state-of-the-art techniques will inspire future researchers.

The following major topics are covered in this book:

- Neurogenetics: Role of genetics in the development and function of the nervous system in schizophrenia patients.
- Neurochemistry: Interface between genetics, brain pathology, and chemical interactions in the brain of schizophrenia patients.
- Neuropharmacology: Implication of drugs and chemical compounds in the brain of schizophrenia patients.
- Psychotherapy: Discussing treatments of schizophrenia using psychotherapy such as intensive cognitive-behavioral therapy and routine care supportive counseling. It will also discuss complementary psychotherapy for patients such as music therapy, art therapy, and others.
- Clinical psychiatric treatment: It will discuss the administration of antipsychotics and clinical intervention of schizophrenia patients.
- Neuroimaging and computational neuroscience: This will throw light on the scope of the study of schizophrenia in terms of computational approaches and medical imaging techniques.
- Social neuroscience.
- Cognitive neuroscience and many more.

Chapter 1 introduces the fundamental concepts of schizophrenia. When traced back, it was found that cognitive and psychological disorders were reported frequently in history. Symptoms of schizophrenia initially were compared and were confused as dementia and were tossed with the same. However, schizophrenia remained an enigma until the early 1900. This chapter introduces the various perspectives of the disorder in all aspects as well as states the recent advancements in all spheres for the diagnosis and treatment of schizophrenia.

Chapter 2 focuses on genetic mutations and alternative splicing in schizophrenia. The chapter tries to explain all possible RNA mis-splicing related to schizophrenia. It lists some genes and their types of splicing, the position of exon-intron skipping, intron retention, alternative promoter, exon inclusion, etc. Transcriptomic analysis demonstrated the genetic risk of schizophrenia in the human brain by using short-read RNA-sequencing.

Chapter 3 describes how the chemical interaction changes in the brain during schizophrenia, also how due to changes in the chemical interactions the structure of the brain changes.

Chapter 4 describes the diagnostic perspective of schizophrenia from the past to the present. It is a mental illness characterized by a combination of symptoms such as perceptual misinterpretation, cognitive impairment, and emotional dysfunction.

Chapter 5 describes various biological conditions to identify a disorder as schizophrenia or not. The symptoms of schizophrenia are broadly divided into two types: Positive and Negative symptoms. In this chapter we have covered five major mental disorders which share some of the other common characteristics. We have selected SZD, Alzheimer's disease, Parkinson's disease, chronic depression, and bipolar disorder. Starting from their definition to its severity we have highlighted different characteristics like biological, psychological, and cognitive characteristics of SZD and how it is different from other disorders. Wherever possible we have also linked more than two disorders and ways to differentiate them from each other.

Chapter 6 describes the neurobiological aspects of Schizophrenia and the Relationship between neurological disorders such as depression, anxiety, and epilepsy. This study identifies the issue neurobiologically more than pathologically or medically as we know. Firstly, schizophrenia causes the nervous system and brain functions such as the cerebrum, cerebellum, white matter, and gray matter. These phenomena are associated with neurotransmitters occurrence even, like dopamine, glutamate, etc. Secondly, depression and anxiety disorder have comparable symptoms physically and mentally.

Chapter 7 states the clinical treatments available for schizophrenia. In this chapter, a combination of all guidelines which is currently followed worldwide is highlighted. To start any treatment, initial assessment of the patient is very important. Following assessment, the aim should the correct diagnosis of schizophrenia. Multiple types of treatment options are available for schizophrenia like pharmacological, ECT, and non-pharmacological. Pharmacological management mainly includes various types of antipsychotics, antidepressants, and benzodiazepines.

Chapter 8 provides insights into the neuropharmacological treatment of schizophrenia from the past, present, and future. Here, we describe the key meta-analytic evidence on the efficacy of antipsychotics in the acute treatment of schizophrenia, particularly clozapine in treatment-resistant patients. In this chapter, primarily we focus on the neuropharmacological treatment options available for schizophrenia and how has the treatment changed over time.

Chapter 9 explains the management of schizophrenia from the clinician's perspective. The pathophysiology of schizophrenia is not completely understood yet; hence there is no definitive treatment for the disorder. Antipsychotics have been the mainstay for the management of schizophrenia since the beginning. Antipsychotics are broadly classified into typical and atypical antipsychotics. All the antipsychotics are associated with extrapyramidal Parkinson-like side effects, more so with typical antipsychotics. Psychotherapy is the newer option for targeting especially the negative symptoms of schizophrenia. Among psychotherapeutic approaches, the most successful approach to date is cognitive-behavioral therapy.

Chapter 10 states the pharmacotherapy and emerging treatment strategies for schizophrenia. Recognizing the clinical manifestations of schizophrenia early is essential. It is caused by genetic factors, alterations in the neurotransmitter system,

mitochondrial dysfunction, immunological variables, and psychological issues. Apart from these causes, traumatic events in childhood or particularly cannabis consumption during adolescence (a critical phase in the development of the brain) may influence the disease's origin, progression, and relapse risk. Initiating early treatment immediately after the initial episode of psychosis is important for recovery. The patients usually require long-term treatment. There are multiple medications available for treating and managing symptoms associated with schizophrenia.

Chapter 11 discusses the alternative therapies available for schizophrenia. People with schizophrenia live a low quality of life because of unfortunate clinical considerations, vagrancy, joblessness, monetary constraints, and inadequate funds to pay for medicals, ignorance, lack of formal education, and unfortunate interactive abilities or social interaction. Because of the amalgamation of various top-notch antipsychotic prescriptions, an incredible headway in its treatment has been made in the last century. This chapter aims to make known and consider the importance of alternative and corresponding strategies and methods in the treatment of schizophrenia.

Chapter 12 states the different phases of schizophrenia patients: from the psychological perspective. The primary purpose of this chapter is to review current clinical staging information in schizophrenia spectrum disorders. In the last two decades, clinical staging has been integrated into psychiatry. Its major purpose is to categorize the disorder's progression into distinct phases based on severity, progression, and disease features to better anticipate outcomes as well as choose appropriate therapeutic interventions.

Chapter 13 states the stigmatizing attitudes towards patients with schizophrenia among medical professionals and the general population. For this study, data was taken from a group of Nonpsychiatric Doctors with over 10 years of experience in their field, a group of the general population having a minimum qualification of a bachelor's degree, and from psychiatrists having a minimum qualification of an MD in Psychiatry. A total of 28 responses from nonpsychiatric Doctors, 27 responses from the educated general population, and 20 responses from psychiatrists were obtained. There were significant differences (with a 95% level of confidence) in the means of stigmatizing attitudes towards people with schizophrenia among Psychiatrists, Nonpsychiatric Doctors, and the General Population. Noticeable stigmatizing attitudes were also seen in mental health professionals.

Chapter 14 talks about the rehabilitation of schizophrenia and practical interventions. The current study was conducted on an individual with schizophrenia who had a cognitive and social deficit. The conclusion was made based on the results of the MMSE to determine the impact of Psycho-Social interventions of CBR in the community. The improvement in the score of cognitive deficit is compiled with the satisfaction of the patient and family members.

Chapter 15 states the consumption of Cannabis and its risk factors as a therapeutic agent for patients with schizophrenia. The consumption of cannabis has repeatedly been linked to the occurrence of psychosis and subsequently, conversion into schizophrenia. The factors that affect the relationship between cannabis use and schizophrenia are dose, age of onset, gender, genetic predisposition, environmental

risk, and comorbid substance use. Many structural and functional alterations occur in the central and peripheral tissues because cannabinoid receptors are stimulated that are found all over the central nervous tissues and in some peripheral tissues. Schizophrenia patients who smoke cannabis have a greater chance of recurrence, extended hospital stays, and exhibit extreme positive manifestations.

Chapter 16 describes the state-of-the-art applications of medical imaging for schizophrenia. In this chapter, we have addressed one of the disorders associated with the human brain, known as schizophrenia. It is a psychotic disorder that makes the person interpret things around the environment abnormally. In the next section, we have enlightened schizophrenia and medical imaging relations, various types of neuroimaging techniques including CT scan, MRI (magnetic resonance imaging), fMRI (functional MRI), PET (positron emission tomography), and comparison among them. Also, we have discussed different machine learning and deep learning frameworks and techniques used in this area. Finally, we have concluded our chapter with the future scope, upcoming challenges, and conclusions.

Chapter 17 explains schizophrenia and its effect on marital satisfaction. This chapter aims to explore how schizophrenia can affect one's marital satisfaction and how marriage can affect any individual diagnosed with schizophrenia. The chapter also aims to understand the relationship shared between spouses and the parent-child dynamic with the parent being diagnosed with schizophrenia. The highlight of this chapter is that we try to understand marital satisfaction in individuals with schizophrenia through the perspective of Sternberg's Triangular Theory of Love. The theory discusses relationships through the help of 3 aspects: Intimacy, Passion, and Commitment.

Chapter 18 states the mortality rate of schizophrenia. The people diagnosed with severe mental illness have a 10–20 years lower life span compared to normal people. Schizophrenic patients have also 15 years of less life expectancy as per new research studies. One study done in 2015 found that patients with schizophrenia are three and half times more likely to die in the given year than people in the same age group. To reduce the mortality among schizophrenic patients, modifying factors like exercise, diet, and substance abuse can be addressed along with the support of family members. The stigma of mental illness and social and economic status play a significant influence on survival and the standard of living among schizophrenic patients.

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Chapter 1
Understanding Schizophrenia: Introductory Aspect of the Mental Disorder from Various Perspectives

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When traced back, it was found that cognitive and psychological disorders were reported frequently in history. Symptoms of schizophrenia initially were compared and were confused as dementia and were tossed with the same. However, schizophrenia remained an enigma until early 1900. It was Eugen Bleuler who used the word Schizophrenia for the very first time in 1911. Diagnosis and treatment of schizophrenia have been a concern for almost every researcher. Different patients experience different prominent symptoms but the major ones are hallucination, delusion, emotional withdrawal, and cognitive impairment. Depending upon the symptoms schizophrenia is further divided into different types of schizophrenia. There have been constant changes in the treatments and ways to diagnose schizophrenia. This chapter introduces the various perspectives of the disorder in all aspects as well as states the recent advancements in all spheres for the diagnosis and treatment of schizophrenia.

1.1 Introduction

Psychosis is a characteristic of schizophrenia that is frequently linked with considerable impairment and can affect all areas of functioning in personal, familial, social, academic, and occupational settings. People suffering from schizophrenia are regularly subjected to stigma, discrimination, and infringement of their human rights. Around the world, every two persons out of three persons experiencing psychosis do not get professional mental health treatment. There are several effective treatment options available, and a minimum of one person out of three persons suffering from schizophrenia may be fully recovered.

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Approximately 24 million people, or 1 in 300 persons, globally suffer from schizophrenia (0.32%). Adults had a rate of 1 in 222 (or 0.45%) at this time. It is not as common as many other mental diseases. The most typical ages for onset are late teens and early twenties, and males often experience onset sooner than females. Key suffering and impairment in personal, familial, social, academic, occupational, and other significant aspects of life are typically linked to schizophrenia. Schizophrenia patients have a two to three times higher risk of dying young than the general population. Physical ailments including viral, metabolic, and cardiovascular problems are frequently to blame for this.

When traced back the evidence of schizophrenia was found in the early eighteenth century. Different psychiatrists, neurologists, and researchers observed different symptoms and suggested different names for the same disorder. Later in the nineteenth century, it was Eugen Bleuler who brought forward the term schizophrenia. Before him, the strongest arguments were presented by Émil Kraepelin (1856–1927) (Haller et al. 2014a; Kyziridis 2005). He called schizophrenia "dementia praecox" based on the symptoms showcased by different patients (Kyziridis 2005).

In a similar line, Kurt Schneider in the year 1959 brought forward a new concept named "First-ranked" symptoms. According to him if a person showcases the following symptoms he/she must be diagnosed with schizophrenia (Cutting 2015).

- A feeling of one's thoughts being spoken aloud.
- A feeling of control over one's behavior and actions.
- A feeling of thoughts being constantly removed and inserted into one's mind.
- A feeling of influence on one's thoughts and control.

Over the past couple of decades, every month has witnessed research on schizophrenia in the field of neurobiology, neurochemistry, neuro-pharmacology, diagnosis, psychology, and genetics. However, even after such intensive research work, we lack answers to many questions related to schizophrenia. In this chapter, we have compiled data to bring a clear picture of what is schizophrenia.

1.2 Symptoms of Schizophrenia

The symptoms observed in patients suffering from schizophrenia are divided into three types (Andreasen and Olsen 1982; Chatterjee and Mittal 2020):

- Positive symptoms.
- Negative symptoms.
- Mixed/cognitive symptoms.

1.2.1 Positive Symptoms

The term "positive" does not mean something good, the term positive is referred to the presence of the symptom. Schizophrenia patients experience many changes in their thinking process and lifestyle; however, there are some specific symptoms like auditory and visual hallucination, delusion thought and memory disorders, and even moving disorders which are visible during schizophrenia. Such symptoms are known as positive symptoms of schizophrenia (Andreasen and Olsen 1982; Chatterjee and Mittal 2020).

1.2.2 Negative Symptoms

The term negative here is referred to the lack or absence of normal human thinking trades. The term negative symptom does not mean something bad or wrong they point out the trades that a person suffering from schizophrenia lack as compared to a healthy subject. In comparison with healthy subjects, it was observed that people suffering from schizophrenia show symptoms like lack of pleasure, difficulty in daily life activities, and struggling with thoughts and concentration (Andreasen and Olsen 1982; Chatterjee and Mittal 2020).

1.2.3 Mixed and Cognitive Symptoms

There have been cases reported where the patient suffers from both negative and positive symptoms. The patient does not show any prominent symptoms out of positive or negative symptoms. Thus, in such cases, it is said that the patient is reporting mixed symptoms (Andreasen and Olsen 1982; Chatterjee and Mittal 2020).

Schizophrenia patients also complain of problems like memory retention and function execution. Such symptoms are termed cognitive symptoms (McCutcheon et al. 2020).

1.3 Causes and Diagnosis of Schizophrenia

After decades of continuous research the following parameters are the major causes listed for schizophrenia (Bansal and Chatterjee 2021):

- Genetics.
- Neurotransmitters.
- Drug abuse.

- Lifestyle.
- Childhood trauma.

However, the exact cause of schizophrenia is still an enigma. To diagnose a patient with schizophrenia and to determine the exact cause the medical professionals look for family history, any childhood trauma, drug abuse, and changes in the neurotransmitter levels. They also record the period of the symptoms. If any of the two prominent symptoms of schizophrenia are observed prominently for more than 6 months, then the patient is diagnosed with schizophrenia. At every lateral stage of the disorder, medical professionals also use brain imaging technology to study the functional and structural changes in the brain.

Among these major causes of schizophrenia, some causes need to be understood in terms of their symptomatic matches with psychosis. Proper diagnosis depends on understanding the root of the disorder. The research has provided fresh insight into the argument over the significance of hereditary and environmental factors in psychotic illnesses. For many years, research in the field of mental health has concentrated on the biological causes of disorders like schizophrenia, bipolar disorder, and psychotic depression. However, there is growing evidence that these disorders cannot be fully understood without first taking into account the experiences of individual patients. However, a few causes are there such as genetic, neurochemical changes in the brain, and drug abuse, which are generally common triggers of schizophrenia.

- *Genetics*: There are instances where schizophrenia runs in families. Although the condition is heritable, more than one gene is not to blame for its spread. It is more likely that someone with a certain gene combination will be susceptible to the illness. 108 genes that are somehow related to the risk of schizophrenia have been found by researchers. Additionally, it was shown that there is twin concordance, meaning that even if identical twins are raised separately, the likelihood of one of them having schizophrenia is 50%. However, the illness's cause is not solely hereditary in nature (Chatterjee and Mittal 2020).
- *Neurotransmitters*: Since some of the symptoms of schizophrenia may be treated with medications that change the number of neurotransmitters, there is an association between neurotransmitters and schizophrenia. Schizophrenia may have its origins in a shift in the levels of serotonin and dopamine (neurotransmitters). Research suggests that disparity between the two may be the root of the issue (Bansal and Chatterjee 2021). Other investigations have demonstrated that schizophrenia is influenced by a change in the body's sensitivity to neurotransmitters.

  Drug abuse: Drug misuse increases the risk of developing schizophrenia or an illness similar to it, according to research, although drugs do not directly cause schizophrenia (Chatterjee and Mittal 2020). Some chemicals, most notably cannabis, cocaine, LSD, or amphetamines, may trigger schizophrenia symptoms in vulnerable people. Cocaine or amphetamine use can lead to psychosis, and individuals who have recovered from a prior episode are at risk of relapsing.

Adolescents and young adults who consistently use cannabis are more likely to develop schizophrenia in their later years, according to a study.

- *Childhood trauma:* Compared to children chosen at random from the community, individuals who received any kind of trauma before the age of 16 had a roughly threefold increased risk of developing psychosis as adults (Bentall et al. 2012). Researchers discovered a link between the severity of trauma and the chance of getting sick later in life. People who experienced severe trauma in childhood were at greater risk than those who just had mild trauma, sometimes up to 50 times more risk.

The specific cause of schizophrenia is unknown. According to a study, if a person has a mix of physical, genetic, psychological, and environmental factors, he or she is more likely to get the condition. A worrying or traumatic life encounter may spark a psychotic outbreak in individuals who are susceptible to schizophrenia. It is unclear why certain individuals get signs, while others do not.

The great majority of persons with schizophrenia do not currently have access to mental health services. An estimated 50% of patients in psychiatric facilities have been diagnosed with schizophrenia. Few individuals who suffer from psychosis receive specialized mental health care. The majority of funds allocated for mental health services are inefficiently used for hospital care. There is overwhelming evidence that mental institutions often violate the fundamental human rights of individuals with schizophrenia and are ineffective at delivering the treatment that those with mental health issues require.

1.4 Perceptions on Schizophrenia

"Schizophrenia." Does this word make you picture aggressive, mentally ill people with several personalities? It does for many people. Mental health groups all across the world are working to dispel these myths about the condition. The above-mentioned data about schizophrenia is a nutshell of the years of research done in this field. Before researchers could conclude anything about schizophrenia everyone had different perceptions about the same.

According to earlier research, those with schizophrenia are more prone to commit violent acts than those without the condition. However, a lot of these studies claim that the major cause of the increased aggression in persons with schizophrenia is a drug and/or alcohol addiction, a condition that can also increase violence in populations who do not have schizophrenia. A patient suffering from any disorder be it physical or mental has always been vulnerable from the start (Lewis and Lieberman 2000). When looking for evidence it was found that the kinds of literature available in Greek, Chinese, Hindu, and Roman had traces of mental disorders. During the ancient age it was believed that either due to physical or mental disorder each human being is abnormal (Kyziridis 2005).

Later from the ancient age to the medieval age, the beliefs remained the same. However, sometime in the seventeenth century, things turned around. Scholars from different areas started talking about different symptoms and the psychiatric approach to them. Shock therapies were given importance which was not the solution (Kyziridis 2005).

Starting from the 1700s to the 1900s was the time for the pioneers of psychiatry. It was during this time that different scholars worked and identified similar symptoms and even divided them into different sets under the psychiatry spectrum. It was in the eighteenth century that researchers observed symptoms like hallucination, delusion, and emotional dullness in people. It was Jean Etienne Esquirol who defined the term hallucination as we know it now. It was in this duration only the researchers could identify that some disorders can be inherited by one through genes. This era helped people to understand the human mind in a better perception (Kyziridis 2005).

The bigger exploration of the human mind and body was done in the nineteenth century. During this era, the scholar looked after patients who showed similar symptoms but late in life. Emil Kraepelin was already working with patients of young age showing some psychological disorder. He names it dementia. It was him in the year 1878 who said if a person is showcasing symptoms like hallucination, delusion, emotional dullness, and some motor disorders then that should be called a case of dementia. Later to distinguish it from other dementia he edited the name to dementia praecox (Ashok et al. 2012).

Until 1911, schizophrenia was known as dementia and was called dementia praecox. Even a few people called it a mad disorder where a person listens to an external voice that in reality is not there. The term dementia praecox was criticized by Eugen Bleuler in the year 1911. He said there is no evidence to call the disorder dementia where a person experiences hallucination or emotional dullness. It was he who tossed the term schizophrenia from the Greek language. According to the Greek language the meaning of schizophrenia is split-mind (schizo—split; phone—mind). He made clear that the term schizophrenia does not mean split personality disorder (Kyziridis 2005; Ashok et al. 2012; Bleuler 1950).

Surprisingly since 1911, the definition of schizophrenia has been changing now and then. Bleuler and Kraepelin joined hands and together worked to explore more about schizophrenia. They together noted different symptoms experienced by various schizophrenia patients and divided schizophrenia into sub-types. Following are the five sub-types of schizophrenia proposed by Bleuler and Kraepelin together (Ashok et al. 2012; Bleuler 1950):

- Paranoid schizophrenia.
- Disorganized schizophrenia.
- Catatonic schizophrenia.
- Undifferentiated schizophrenia.
- Residual schizophrenia.

After an outstanding contribution, different researchers and scholars came together and along with Bleuler coined the term positive and negative symptoms of schizophrenia. It is discussed in Sect. 1.2.

After the identification of the disorder and defining it in the best way possible, it was time for its treatment. However, the absence of the exact cause of schizophrenia was hard for the researchers to conclude.

1.4.1 Negative Perceptions of Schizophrenia

Unsurprisingly, schizophrenia sufferers may be prevented from receiving the care and social support they require due to society's unfavorable opinions of those with the condition. The stigma associated with a schizophrenia diagnosis hinders access to care and social assistance in other ways as well. It may make it more difficult for those who have schizophrenia to lead happy lives. It appears that eradicating the stigma connected to schizophrenia is receiving more attention than ever. Worldwide organizations are making a lot of effort to inform the public about schizophrenia. There is some evidence to support the idea that this focus is altering public perceptions of the illness. Although views and knowledge about many illnesses, such as bipolar disorder and depression, have changed significantly, this does not appear to be the case with schizophrenia.

Social psychology research has extensively examined the elements and mechanisms behind majority groups' attitudes toward marginalized minority groups as well as, more recently, the attitudes of minority group members toward both their group and the majority. People with schizophrenia are frequently the targets of overwhelmingly unfavorable attitudes and actions, and they are also acutely aware of the stigma attached to their participation in this group. One of the things that appear to contribute to worsening the inadequate social functioning of those with schizophrenia is the awareness of how other people view them. According to recent research, stereotypes linked with other stigmatized groups are significantly responsible for how persons with schizophrenia are seen by other groups (Castelli et al. 2021).

1.4.2 Perceptions of Schizophrenia in Later Life

The demographics of older persons (defined as those 55 years and over) with schizophrenia have radically altered globally over the past several decades in terms of the definite numbers afflicted, the overall percentage of people who have the condition, life expectancy, and societal settlement. The elderly population with schizophrenia has enormous healthcare demands, and their medical comorbidity raises death rates over those of the normal population. The understanding that concomitant medical and neurological illnesses might impact psychotic conditions in later life should temper suggestions to categorize the disorder into three categories, such as, "early-onset," "late-onset," and "very-late-onset" categories. With an understanding that numerous outcomes can occur, mostly independently of one

another, and that they require varied treatment techniques, the idea of outcome has grown more sophisticated. Numerous cutting-edge non-pharmacological therapy modalities have been developed to supplement therapeutic alternatives for the unique requirements of elderly schizophrenia patients (Cohen et al. 2015).

1.4.3 Psychodynamic Perspectives of Schizophrenia

According to early psychoanalytic, theories of psychosis and psychotic conditions are a result of the unconscious and dreams invading the waking consciousness (Lincoln et al. 2013). Modern methods emphasize the significance of early connection patterns. There is an assumption that internal representations of past and present connections create tension, and that psychotic symptoms are a healthy method to release this strain. Focusing on these processes, psychodynamic therapy promotes new, healthy relationships by assisting the patient in developing self-awareness and comprehension of the impact of previous conduct on present behavior. Early psychoanalytic notions (such as the stereotype of the schizophrenogenic mother) and the idea of double-bind communication, which refers to parental communication that is paradoxical (rejecting while seeking affection), have not been proven to be accurate by subsequent studies (Lincoln and Pedersen 2019; Maaßen et al. 2021). Additionally, research has usually indicated that individuals with schizophrenia frequently do not respond well to insight-oriented psychotherapies due to their problems with self-reflection and abstract cognition as a result of their mental disorder.

1.4.4 Cognitive Perspective of Schizophrenia

When we consider the primary signs and symptoms of psychotic illnesses like schizophrenia, we picture a person who may have delusions, hear voices, and see images. However, cognitive issues are also a significant component of psychotic diseases in general and schizophrenia in particular (Green 2006). The focus on cognition in schizophrenia has been influenced by the growing body of research showing that cognitive problems in schizophrenia are a major contributor to impairment and loss of functional competence. Schizophrenia is characterized by a wide range of cognitive abnormalities, including difficulties with working memory (Chatterjee et al. 2019), episodic memory, and other activities requiring behavior control or regulation. In addition to having issues with processing speed, people with schizophrenia usually do practically all activities more slowly than healthy people. The fact that these cognitive deficiencies exist before the start of the illness and also exist in first-degree relatives of patients with schizophrenia, albeit in a weaker form, is significant.

1.4.5 Humanistic Perspectives of Schizophrenia

In client-centered or humanistic treatment, it is believed that unconditional positive regard, accurate empathy, and sincerity can assist a patient to improve the similarity between the true and perfect selves. According to Rogers and colleagues, everyone has an innate desire to advance personally and realize their full potential (Rogers 1967). The symptoms of psychosis are viewed under this perspective as a distorted version of this actualizing propensity. In client-centered treatment, the relief of certain symptoms comes second and is less important than personal experiences. As a consequence, no specific treatment strategies for psychosis have been devised. Conversely, this strategy advises therapists to pay close attention to the client's viewpoint, make sure the patient is heard and put a strong emphasis on the human relationship (Truax 1970).

1.4.6 Sociocultural Perspective of Schizophrenia

A variety of environmental variables are also linked to an elevated risk of schizophrenia development. For instance, a higher risk of schizophrenia has been linked to pregnancy issues such as increased stress, infection, malnutrition, and/or diabetes (Cannon et al. 2002). In addition, there is a link between a child's chance of developing schizophrenia and birth-related difficulties that result in hypoxia (short of oxygen). Additionally, there is a little increase in the chance of developing schizophrenia in children whose fathers are older (Bourque et al. 2011). Additionally, cannabis use raises the likelihood of psychosis, particularly when combined with other risk factors (Casadio et al. 2011). Children who grow up in metropolitan environments also have a higher risk of getting schizophrenia. These two characteristics could indicate more societal and environmental pressure in these environments. The majority of those with these risk factors do not go on to develop schizophrenia, but sadly none of them are precise enough to be helpful in a clinical environment. Together, they are starting to provide us with hints about the neurodevelopmental characteristics that would make someone more likely to acquire this illness.

1.4.7 Cross-Cultural Perspectives and Influences of Culture on Schizophrenia

The way we perceive mental health illnesses and the associated symptoms are influenced by culture. There are societies all across the world that do not view symptoms of schizophrenia-like hearing voices (hallucinations) as abnormal, including Peru. Instead, they may even be viewed as unique skills and links to the spirit

world, with the person who hears voices potentially becoming the local Shaman or medicine man. Those that fall under this category assist others and themselves in finding understanding and healing. The same characteristic of hearing voices would be seen as aberrant and an indication of an underlying illness such as schizophrenia in Western countries. A person displaying these symptoms would not be held in a position of awe or adoration, but would most likely be admitted to a hospital or treatment center for additional care and therapy to control and lessen the shown symptoms.

1.4.8 Cognitive-Behavioral Perspective Schizophrenia

The foundation of cognitive-behavioral treatments for psychosis (CBTp) is the idea that the spectrum of normal experiences includes psychotic symptoms. They are also supported by research that suggests that normal if heightened, systems of perception and cognition are the source of psychotic experiences. Cognitive theories of psychosis have been built on the foundation of this insight. The majority of descriptions within the cognitive-behavioral interventions for psychosis (CBTp) framework emphasize the value of creating a long-lasting healing relationship through the processes of listening and validating, working collaboratively, and using an individual case formulation. Other crucial components include the use of cognitive and behavioral therapies to treat psychotic conditions along with altering malfunction beliefs and avoiding recurrence.

1.5 Recent Advancement in Schizophrenia

In the past when schizophrenia was investigated and rolled out the biggest setback was the availability of resources. Many aspects were left unanswered but with the advancement, in the field of science and technology, those questions are answered.

Earlier the causes of schizophrenia were identified depending on the patients' lifestyle and family history but now with the help of science and technology, researchers have identified the exact gene which could be responsible for causing schizophrenia if it is inherited. The researchers have concluded the role of different neurotransmitters in causing schizophrenia. Hypotheses like dopamine hypothesis, glutamate hypothesis, and serotonin hypothesis have been proposed with evidence (Bansal and Chatterjee 2021). The effect of drugs on the human brain has been studied.

The researchers now emphasize the functional and structural alterations in the human brain during schizophrenia. With the help of brain imaging techniques such as Computed-Tomography (CT) scans, Positron Emission Tomography (PET) scans, Magnetic Resonance Imaging (MRI), Functional MRI (fMRI), and researchers have various brain images. According to the studies done using these

images, the researchers have highlighted some major points (Chatterjee and Mittal 2020; Chatterjee et al. 2020a; Joo et al. 2021).

- Gray matter reduction in various parts of the brain.
- Abnormalities in the white matter in different places are observed.
- Changes in the level of different neurotransmitters in the human brain.
- Age and gender play a vital role in schizophrenia severity.
- Enlarged ventricular are observed.

Apart from these, the recent focus on various techniques and translational bio-behavioral investigation sphere requirements might potentially contribute to the development of a schizophrenia diagnosis based on neuroscience. Today, it is believed that several small-effect and less large-effect susceptibility genes combine with a variety of natural or environmental variables to cause schizophrenia. These elements might cause neuroplasticity to change in a way that is developmentally mediated, starting around the time of early adolescence and showing up as a cascade of neurotransmitter and circuit dysfunctions along with reduced connectivity. This newfound understanding of etiopathology has sparked a renewed hunt for cutting-edge pharmacological and psychotherapy targets. High-priority objectives for the discipline include creating hypothesis-driven early therapies and preventative techniques in addition to addressing the fundamental aspects of the condition, such as cognitive deficiencies and unpleasant symptoms.

Recent research has provided persuasive evidence that neuropathological alterations in schizophrenia may begin to develop just before the commencement of psychotic symptoms, during the crucial adolescent years. Declines in gray matter seem to start in the initial stages of schizophrenia and may be linked to worse results (Chatterjee et al. 2020a). Presynaptic dopamine turnover and glutamatergic activity elevations may both be linked to the early stages of psychosis. These findings emphasize the significance of early detection and treatment aimed at the pathophysiological processes just before the onset of psychosis.

According to neuropathology studies, schizophrenia is characterized by aberrant prefrontal network development in the late teenage years and early adulthood, most likely as a result of excessive synaptic and dendritic spine pruning (Feinberg 1982). Pre- and postsynaptic defects in inhibitory neurons, like parvalbumin interneuron, might impede these crucial phases of neurodevelopment. Parvalbumin interneurons may affect gamma oscillations, which are linked to cognitive function, according to recent optogenetic research. According to post-mortem studies that show the decreased manifestation of myelin basic protein in cortical areas, myelination is also aberrant in schizophrenia (Haller et al. 2014b). Recent developments in neuropathology add to earlier post-mortem studies that showed diminished neuropil but not fewer neurons in schizophrenia-affected individuals' brains (Sohal et al. 2009; Matthews et al. 2012).

We have made significant progress in our knowledge of the neurobiology of schizophrenia, thanks to a variety of imaging research methods. The third and lateral ventricles are larger in studies, and there have also been reports of small decreases in the sizes of the limbic, frontal, and whole-brain gray matter, as well as the temporal,

frontal, and third ventricles (Chatterjee et al. 2020a). In functional MRI investigations, the dorsolateral prefrontal cortex was shown to be less active during executive function activities and the limbic system to be activated abnormally during tasks requiring emotional inputs (Chatterjee 2018; Chatterjee et al. 2020b). The frontal and temporal lobes have shown indications of white matter alterations in studies utilizing diffusion tensor imaging, a technique for examining the white matter, which would suggest a diminished connection between these areas. The interpretation of neuroimaging results in the clinical context is the next significant difficulty. To uncover biomarkers that may be helpful for clinical diagnosis and therapy, a new investigation has started to incorporate a variety of imaging modalities with genetic, electrophysiological, and clinical data.

Since the invention of chlorpromazine, antipsychotic medications have been the foundation of schizophrenia therapy, concentrating on reducing the frequency and intensity of psychotic occurrences along with enhancing the functioning ability of people with schizophrenia (Chatterjee and Mittal 2020; Bansal and Chatterjee 2021). Second-generation antipsychotics (SGAs), which are typically linked with diminished extrapyramidal symptoms (EPSs) as equated to first-generation antipsychotics (FGAs), were developed in response to the negative effects and suboptimal results linked with FGAs (Swartz et al. 2007). This is because SGAs antagonize 5HT-2A (Leucht et al. 2009). The classification of FGA and SGAs is controversial, though; some research relies on their antagonistic effects on the dopamine D-2 receptors, while others base it on their capacity to produce EPSs. There is no conclusive evidence to support the claim that SGAs are superior to FGAs among first-episode patients or chronic patients in terms of positive, cognitive, or social outcomes. Strong empirical evidence supports the use of clozapine for treatment-resistant positive symptoms, aggression, and suicidal behaviors as well as FGAs and SGAs in acute and maintenance therapy of schizophrenia, according to the Schizophrenia Patient Outcome Research Team (PORT) (Kreyenbuhl et al. 2010).

To improve medication reaction prediction and minimize drug-induced adverse impacts, pharmacogenomics, a burgeoning subject in the treatment of schizophrenia, may help psychiatry move closer to evidence-based customized therapy. For instance, dopamine D3 receptor polymorphisms are related to responsiveness to clozapine and olanzapine, while D2 variations are connected with the efficacy of risperidone (Arranz et al. 2011). Polymorphisms in the serotonergic system are also linked with the effectiveness of clozapine and risperidone. Pharmacogenomics has advanced, yet despite this, it still faces challenges including replication discrepancies, modest research sizes, and a dearth of randomized control trials (Haller et al. 2014b).

1.6 Conclusions

In conclusion, even though our knowledge of the origins and therapies for schizophrenia is still restricted, some significant paradigm shifts have taken place. The diagnosis of schizophrenia is still dependent on symptoms, although psychotic, affective, and developmental illnesses have many hereditary and neurological commonalities. Future categorizations of these disorders should thus shift in favor of more empirically supported, rationally supported, and physiologically based categories and characteristics. It is now known that developmental processes alter neuroplasticity, which manifests as several neurotransmitter and circuit dysfunctions that start to show up around adolescence. Etiology is currently understood to be the result of interactions between several small-effect genes, a few uncommon large-effect genes, and unidentified environmental variables.

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Chapter 2
Genetic Mutations and Alternative Splicing in Schizophrenia

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2.1 What Is Neurogenetics? Related Disease and Disorder

The study of the function of genetics in the evolution and physiology of the brain is called neurogenetics. It was coined to encompass two large fields of study and clinical practice: Genetics and Neurology. An investigation of the link between the genetic code and peripheral nervous system growth and performance, such as personal attributes, behavior, and neurological diseases is the new discipline in neurogenetics (Silva et al. 2021).

2.1.1 Neurogenetic Diseases

Dysfunction of the central and peripheral nervous systems induced by molecular abnormalities in genetic material (DNA) is called neurogenetic diseases. The classification of neurogenetic disease is based on the therapeutic abnormalities or origin and inheritance pattern of hereditary defects. The classification of genetics is utilized with each class having examples of clinical syndromes.

1. During birth, frequent problems cause in numerous organs by chromosomal abnormalities. It may cause different types of chromosomal abnormalities like deletions, duplications, translocations, and ring chromosomes. Down syndrome (trisomy 21), Cri du Chat (5p-), and Miller-Dieker Lissencephaly Syndrome (17p-) are examples.

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2. Nucleotide variations in DNA, like nonsense, deletions, and duplications of one or more nucleotide bases are categorized in the Mendelian group of neurogenetic diseases. If the clinical condition is present in heterozygous carriers of a single mutation, the disease is inherited as an autosomal dominant disorder, e.g., Huntington's disease, Myotonic muscular dystrophy, Fascioscapulo-humoral muscular dystrophy, tuberous sclerosis, Charcot-Marie-Tooth hereditary neuropathy, familial spastic paraplegia, and hereditary ataxias (Bird and Jayadev 2019). Examples of autosomal recessive diseases are Friedreich's ataxia, Tay-Sachs disease, Neimann Pick diseases, and phenylketonuria. x-linked inheritance produced by transitions on the X chromosome and the symptoms of this disease are more significant in males than in females. Duchenne's muscular dystrophy, Pelizaeus-Merzbacher leukodystrophy, and x-linked Charcot-Marie-Tooth hereditary neuropathy are the diseases included in x-linked inheritance. Abnormally massive expansions of regularly occurring nucleotide repeats produce a subset of neurogenetic disorders called as nucleotide repeat expansions. Trinucleotide is present numerously, CAG often.
3. Mitochondrial DNA mutations are passed from generation to generation from the mother's egg cytoplasm. The mutation will be passed on to all children of a mother who has it. Males with the mutation, however, do not transmit the mutated gene on to their children. The quantity of mitochondria with the relevant mutation in any given tissue determines whether or not the individual manifests clinical indications of the mutation (heteroplasmy). Mitochondrial illnesses are characterized by a wide range of indications and symptoms, including cognitive difficulties, seizures, vision loss, hearing loss, peripheral neuropathy, and myopathy. MELAS (mitochondrial encephalomyopathy with lactic acidosis and stroke), MERRF (myoclonic epilepsy with ragged red fibers), and NARP (mitochondrial encephalomyopathy with ragged red fibers) are a few examples (neuropathy, ataxia, and retinitis pigmentosa).
4. Individual neurogenetic illnesses caused by autosomal, x-linked, or mitochondrial mutations are all uncommon. Many prevalent neurological illnesses, however, have significant genetic components to their development. They are thought to be the result of various genes (polygenic) interacting with a variety of environmental circumstances (multifactorial). Alzheimer's disease, Parkinson's disease, epilepsy, stroke, and multiple sclerosis are just a few examples. Rare variants of the disease are caused by recognized mutations in single genes in some cases (e.g., Alzheimer's, Parkinson's, and epilepsy), but the more prevalent form of the disease in the general population is assumed to be polygenic/multifactorial. The various genes and environmental influences in most cases are unknown. However, genome-wide association studies are starting to uncover a slew of potential candidate genes for these frequent complicated disorders.

2.1.2 Neurogenetic Disorders

Related to the nervous system there are several hereditary disorders. The most prevalent types of neurogenetic disorders are nucleotide variations in genes. These disorders include myotonic syndromes, muscular dystrophies, and motor neuron disease. In some neurogenetic disorders, such as Prader–Willi syndrome and Angelman's syndrome, genetic imprinting can be found. There is a distortion on chromosome 15 in both of these disorders, causing autosomal genes to express differently depending on their parental origin (interruption of the gene from mother in Prader-Willi syndrome and in case of Angelman's syndrome disruption of the gene from father). Hereditary motor and sensory neuropathy can be caused by a duplication of a region of chromosome 17, which contains the peripheral myelin protein 22 gene coding. A neurogenetic disorder with gene deletions is hereditary neuropathy with a proclivity for pressure palsies. A loss of chromosome 17 causes this condition. The peripheral myelin protein 22 gene is coded for by this significant deletion. Recurrent focal entrapment neuropathies can develop in those who are affected. Other ailments that can be caused by mitochondrial genome and nuclear-coded gene abnormalities include mitochondrial disorders. Trinucleotide repeat diseases are another type of neurogenetic disorder. Certain abnormalities can be caused by an expanded and aberrant triplet repeat in the DNA. Trinucleotide repeat disorders include Friedreich's ataxia and Huntington's disease. Because modern genetic researching techniques have been established and are now being developed, uncovering the genetic basis of various neurological disorders may be conceivable as a result of these discoveries, which leads to a better understanding of some neurogenetic pathologies (Saberi 2020).

2.2 Schizophrenia and Genetics

2.2.1 Schizophrenia

Schizophrenia is a chronic mental health illness marked by a variety of symptoms such as delusions, hallucinations, disorganized speech or behavior, and cognitive impairment. For many patients and their families, the disease's early start and chronic duration make it a devastating affliction. Negative symptoms (marked by loss or deficiencies) and cognitive symptoms (such as impairments in attention, working memory, or executive function) are common causes of disability. Relapse can also happen as a result of positive symptoms like suspicion, delusions, and hallucinations. Because of the disorder's inherent variety, there is a lack of agreement on clinical guidelines, epidemiology, and pathophysiology (Goldstone 2020).

2.2.2 Genetics

Genetics is a significant risk factor for schizophrenia. During the last decade, genetic analysis research has yielded groundbreaking results, fueling hope for uncovering the basic causes of schizophrenia. However, because of the complexity of the subject of study, it is nearly hard for non-geneticists (e.g., many physicians and researchers) to grasp and appreciate genetic discoveries and their implications. The major risk factor for schizophrenia is thought to be genes (Henriksen et al. 2017). The investigations helped to disprove the psychoanalytical theory of schizophrenic causation, which claimed that schizophrenogenic upbringing was either a necessary or sufficient reason for developing schizophrenia. Twin studies are being done on a molecular level because MZ twins and DZ twins, who share 100% and 50% of their genes, respectively, live in the same environment. Genetic similarity is most likely to account for the greater rates of MZ twins than DZ twins. According to estimates of schizophrenia correlation rates depending on European twin research from 1963 to 1987, MZ twins have a greater rate (48%) than DZ twins (Wolf 2018). According to a meta-analysis (Sullivan et al. 2003) of twin research, genetic vulnerability to schizophrenia is 81% (95% CI, 73%–90%), while shared environmental effects are 11% (95% CI, 3%–19%). Finally, a few investigations of children of discordant MZ twins discovered a significant risk of psychotic symptoms in the symptomatic and asymptomatic MZ twins (Kringlen and Cramer 1989), implying that unaffected MZ twins have silent (non-expressed) schizophrenia susceptibility genes. In the case of discordant DZ twins, however, the risk was larger in the affected DZ twin's offspring than in the unaffected DZ twin's children (Gottesman 1989).

The Human Genome Project (1990–2003) was essential in schizophrenia molecular genetic research. The Human Genome Project was a worldwide academic project aimed at determining the sequence of the 3 billion base pairs that make up the human genome, as well as mapping all of its genes. "Linkage analysis" was the first DNA-based technique, and it attempted to find genomic areas in samples of affected extended or nuclear families and sibling pairs without using a specific allelic mutation. Estimates of linkage between the illness and genomic loci were determined by analyzing the degree of co-segregation of genetic markers and established phenotypic features (e.g., schizophrenia spectrum diagnosis). Linkage analysis is based on the finding that genetic markers that are physically close together on the same chromosome are more likely to be inherited together, i.e., they stay "linked" during meiosis. Numerous schizophrenia linkage studies have been carried out; however, good results have often proven difficult to duplicate in future investigations (Risch and Merikangas 1996). The "candidate gene" strategy was used in the following wave of molecular genetic studies in schizophrenia, which used a case–control study design to see if putative susceptible genes were linked to the condition. The candidate gene approach, unlike linkage analysis, can detect genes with minor effect alleles if the sample size is large enough. Candidate genes are usually chosen based on their location (e.g., results from linkage analysis) or functioning (e.g.,

genes coding for proteins related to dopamine or serotonin neurotransmission). DISC1, DTNBP1, NRG1, and COMT are some of the most commonly mentioned candidate genes; however, their possible pathogenetic role in schizophrenia is still being contested. In contrast to the hypothesis-driven candidate gene approach, which can only test a few genetic markers in constrained genomic loci in each study, genome-wide association studies (GWAS), which often use a case–control study design, look for associations between common genomic variants or loci and the disorder purely empirically (i.e., GWAS do not rely on any a priori selected candidate genes). The International HapMap Project and the 1000 Genomes Project (continued by The International Genome Sample Resource) have made it possible to identify and map millions of common single nucleotide polymorphisms (SNPs), which has aided the GWAS technique. Linkage disequilibrium, or a non-random connection of alleles at two or more loci, provides the basis for GWAS. The GWAS methodology is based on the "common-disease common-variants" theory, which claims that schizophrenia is mostly caused by common genetic variants (SNPs) (Henriksen et al. 2017). Common genetic variants appear to account for just a portion of the variance in genetic liability. The "common-disease rare variants" hypothesis (McClellan et al. 2007) posits that highly penetrant, rare (1% of the population) genetic variants, such as copy number variations (CNVs), single nucleotide variants (SNVs), and minor insertions and deletions (indels), contribute to the genetic basis of schizophrenia. There are two hypothesis:

1. CNVs, which are structural genomic variations that primarily consist of duplication or deletion and are either de novo (i.e., new and not inherited) or hereditary, give a significant risk for schizophrenia. CNVs might be one kilobase (kb) or several megabase (Mb) pairs in size. In comparison to controls, people with schizophrenia had higher amounts of uncommon CNVs, according to several studies (Chang et al. 2016; Szatkiewicz et al. 2014; Ruderfer et al. 2016; Girirajan and Eichler 2011; Stone et al. 2008).
2. A method that enables the detection of DNA changes inside the 1% protein-coding sections or genes (exons) of the genome (the exome) has allowed single-base resolution scans of genes for variations that were previously undetectable, such as SNVs and indels. Exome sequencing is justified by the fact that changes in these regions are more likely to have serious implications than changes in the remaining 99% of the genome. Exome sequencing has now been utilized to investigate SNVs and indels in schizophrenia in a number of research. Certain studies have found that patients with schizophrenia have a slightly higher exome-wide level of uncommon and/or de novo SNVs than controls, although this conclusion has not been reproduced in other research (Xu et al. 2012; McCarthy et al. 2014). The glutamatergic postsynaptic proteins ARC (activity-regulated cytoskeleton-associated protein) and N-methyl-D-aspartate receptor (NMDAR) postsynaptic protein complexes, which have previously been linked to schizophrenia in CNV studies (Glessner et al. 2010) were found to be significantly enriched in de novo SNVs and indels. Finally, researchers employed exome sequencing to look for uncommon SNVs and indels in schizophrenia and

discovered a polygenic load of very rare (1/10,000) disruptive variations spread across multiple genes in a set of 2546 genes previously linked to schizophrenia by GWAS, CNV, and de novo SNV studies (Aguila et al. 2013).

2.3 Genetic Mutations and How They Are Responsible to Cause Schizophrenia

Synapsin III, a 22q13-linked gene, is a positional target gene for schizophrenia (SZ). In the promoter region of synapsin III, one interesting single nucleotide polymorphism (SNP), −196G/A, has been discovered. The –196A allele has a 6/8 base match to Oct-1's core recognition octamer sequence, which belongs to the POU transcription factor family (Lachman et al. 2006).

To study the nature of the pleiotropic effects of uncommon coding variations on schizophrenia and NDDs, scientist analyzed sequencing data from schizophrenia and new large NDD datasets. Given that neurodevelopmental damage in NDDs is often more severe than in schizophrenia, scientist (Owen et al. 2011) hypothesized that pleiotropic genes would be more enriched for a more severe class of mutation in NDDs than in schizophrenia. Interestingly, genes enriched for certain classes of de novo variant in persons with NDDs were also enriched for congruent variant classes in people with schizophrenia, contrary to expectations (Rey et al. 2020).

TSPAN7 (Tetraspanin 7) mutations are connected to X-linked physiological disorder (Zemni et al. 2000; Da Costa Maranduba et al. 2004). TSPAN18 (Tetraspanin 18) is involved in SCZ susceptibility. Researchers also found no statistically significant connection between SCZ and the two TSPAN18 SNPs rs11038167 and rs11038172 in this Han Chinese case–control research. Their findings demonstrate a statistically significant difference between patients with schizophrenia and healthy controls: the frequency of the rs835784 "A" allele occurs at 31% in SCZ samples and 27% in controls. Carriers of the A-allele of rs835784 have a 1.197-fold higher risk of SCZ than non-carriers, according to this study (Yue et al. 2011).

The majority of the genetic risk for schizophrenia is due to inherited genes. De novo mutations in the form of substantial chromosomal copy number alterations, however, occur in a limited percentage of cases and disrupt genes encoding postsynaptic proteins disproportionately. Small de novo mutations affecting one or a few nucleotides are overrepresented in glutamatergic postsynaptic proteins such as activity-regulated cytoskeleton-associated protein (ARC) and N-methyl-D-aspartate receptor (NMDAR) complexes, according to this study. Proteins that interact with these complexes to alter synaptic strength, such as proteins that regulate actin filament dynamics and those whose messenger RNAs are targets of the (FMRP) fragile X mental retardation protein, are also enriched in mutations. Variations in schizophrenia affect genes that are also altered in autism and intellectual disability, as well as mutation-enriched synaptic pathways. Scientists demonstrate replicable

insights into etiological pathways for schizophrenia and reveal pathophysiology common with other neurodevelopmental disorders by combining their observation with a comparable case–control research (Fromer et al. 2014).

For affected individuals and families, rare mutations linked to schizophrenia are highly varied and secretive. Detecting these mutations can aid in establishing a molecular diagnosis, elucidating the pathophysiology, and providing helpful genetic counseling to patients and their families. In a two-generation multiplex family, we used whole-exome sequencing to look for uncommon pathogenic variants cosegregating with schizophrenia and transmitted in a dominant inheritance pattern. We discovered an uncommon missense mutation in KMT2C (lysine methyltransferase 2C) called H1574R (Histidine1574Arginine, rs199796552) that co-segregates with affected individuals in this family. The mutation is a unique detrimental KMT2C mutation. The KMT2C gene encodes a histone 3 lysine 4 (H3K4)-specific methyltransferase that regulates brain gene expression through epigenetic control. Neurodevelopmental problems such as Kleefstra syndrome, intellectual disability, and autism spectrum disorders have been linked to KMT2C mutations. Their results indicate that schizophrenia could be one of the clinical phenotypic spectra of KMT2C mutations, and that KMT2C could be a new schizophrenia risk gene (Chen et al. 2021a, b).

Researchers used whole-genome sequencing to look at two multiplex families with schizophrenia (SZ) and bipolar disorder (BD) as the main inheritance. In one three-generation multiplex family, they discovered a G327E mutation of SCN9A and an A654V mutation of DPP4 cosegregating with SZ and BD. In another two-generation multiplex family, they found three variants cosegregating with SZ and BD: L711S of SCN9A, M4554I of ABCA13, and P159L of SYT14. These five missense mutations were uncommon and harmful. SCN9A mutations have been linked to congenital insensitivity to pain and neuropathic pain disorders in the past. Further research revealed that rare SCN9A mutations are linked to seizures and autism spectrum disorders (Chen and Huang 2021). BSN (bassoon presynaptic cytomatrix protein) missense variant Arg1087Gln cosegregating with schizophrenia in a family with numerous affected members. In addition, researchers discovered an uncommon missense mutation in PCLO (piccolo presynaptic cytomatrix protein) Ser1535Leu in two sisters with bipolar disorder and another rare missense mutation in PCLO, His5142Arg, in a patient with schizophrenia. These three missense variations were thought to be harmful but were pretty uncommon. The BSN and PCLO genes encode two structurally related proteins that regulate neurotransmission at the presynaptic neuronal terminal and are found in the active zone of the presynaptic cytomatrix. Our findings imply that the presynaptic matrix plays a role in the pathophysiology of schizophrenia and bipolar disorder, and that BSN and PCLO are risk genes for both disorders (Chen et al. 2021a, b).

2.4 RNA Splicing and Miss-Splicing (Introduction)

The study of RNA splicing has had an impact on a variety of biological domains. The discovery of several types of splicing, such as alternative splicing, trans-splicing, and self-splicing sequences, has given researchers fresh insights into the increasingly complex web of gene regulation and genome evolution. Investigations into the molecular mechanics of eukaryotic gene splicing have revealed a sophisticated cellular machinery that is responsible for the 'splicing' process. Splicing is also linked to a vast variety of genetic disorders because it is required for the expression of nearly all human genes. The spliceosome is tasked with two opposing tasks: precise and efficient intron excision while remaining flexible enough to allow for the regulation of alternate exon use. Small changes in either pre-mRNA sequences that direct splicing or the machinery that identifies these sequences will result in altered gene expression, which may result in disease, if this balance is maintained. Mis-splicing has been linked to a variety of human diseases, which have been linked to mutations in cis-RNA splicing components of pre-mRNA or mutations in trans-acting proteins. Shortly after splicing was discovered, it was revealed that some splice products of specific gene transcripts used different splice sites, resulting in various mRNA sequences. "Alternative splicing" was coined to describe these phenomena (Jurica and Roybal 2013).

2.5 Genes Involved in RNA Miss-Splicing to Increase Schizophrenia Risk

There are 108 genes responsible to cause schizophrenia among them some are involved in splicing defects and are listed below (Table 2.1).

2.6 How RNA Miss-Splicing (Alternative Splicing) Related to Schizophrenia?

Genes like DRD2, GRM3, and DISC1 have been thoroughly studied in alternative splicing of schizophrenia risk. Many "local splicing" events (e.g., exon skipping junctions) associated with genetic risk of schizophrenia have been discovered by transcriptomic analyses in human brains using short-read RNA-sequencing, and further molecular characterizations have identified novel spliced isoforms, such as AS3MTd2d3 and ZNF804AE3E4. In vitro and in vivo studies of KCNH2–3.1 and Ube3a1 have offered instances for exploring such spliced isoforms (Zhang et al. 2021). Suggested that to study the genetics risk for schizophrenia, alternative splicing may be an important molecular mechanism. Multiple single nucleotide polymorphisms (SNPs) have been linked to this disorder in genetic research,

Table 2.1 The genes involved in RNA miss-splicing to increase schizophrenia risk, few genes, their full forms and types of splicing

Sr. no.	Gene	Full forms of genes	Types of splicing
1	DRD2	Dopamine receptor D_2	Full length Sixth exon skipping
2	GAD1	Glutamate decarboxylase 1	Full length Alternative 3′ exon
3	GRM3	Glutamate metabotropic receptor 3	Full length Exon 4 skipping
4	ZDHHC8	Zinc finger DHHC-type palmitoyltransferase 8	Full length Intron 4 retention
5	NRXN1	Neurexin-1-alpha	Alternative promoter
6	NRG1	Neuregulin 1	Alternative 5′ exon Alternative 3′ exon Exon skipping
7	NRG3	Neuregulin 3	Alternative 5′ exon Exon skipping
8	ErbB4	Erb-B2 receptor tyrosine kinase 4	Exon 16 inclusion Exon 15b inclusion Exon 26 inclusion Exon 26 skipping
9	DISC1	Disrupted in schizophrenia 1	Exon 3 skipping Exon 7,8 skipping Alternative 3′ exon
10	TrkB	Tyrosine protein kinase gene	Full length Alternative 3′ exon Alternative 3′ exon
11	BDNF	Brain derived neurotrophic factor	Alternative 5′ exon
12	Ppp1R1B	Protein phosphatase 1 regulatory inhibitor subunit 1B	Full length Alternative 5′ exon

This table shows the genes involved in RNA miss-splicing to increase schizophrenia risk, few genes, their full forms and types of splicing

including genome-wide association studies (GWASs), (Consortium 2015; Pevzner 2017a, b). A rising body of evidence suggests that schizophrenia risk is linked to mRNA expression in human brains (French and Edwards 2020; Edwards et al. 2013; Chang et al. 2021; Yang et al. 2020). Many dysregulated genes linked to schizophrenia have been discovered to analyze the expression of mRNA using some techniques like real-time quantitative PCR, microarray, or RNA-sequencing (Reble et al. 2018). The majority of multi-exon genes in the human genome are alternatively spliced during transcription, resulting in cassette exons, microexons, intron retention, alternative 5′ and 3′ splice sites, alternative promoters, and alternative untranslated regions (UTRs), as well as diverse transcriptomes, proteomes, and phenomes (Wang et al. 2008; Park et al. 2018). In the brain, alternative splicing is a complicated process. The etiology of brain illnesses may be influenced by the

splicing of specific genes. For example, Gomafu has a long noncoding RNA whose expression is reduced in postmortem brains of schizophrenia patients' and acts as a scaffold for splicing factors like serine/arginine-rich SF1, and Gomafu knockdown promotes the expression of schizophrenia-associated ErbB4 and DISC1 isoforms (Barry et al. 2014). In schizophrenia patients, there was a considerable abundance of switched transcripts containing microexons (Gandal et al. 2018) (Fig. 2.1).

2.7 Treatment

According to growing research and clinical data, schizophrenia is caused by a number of neurodevelopmental issues, including dopaminergic, glutamatergic, serotonergic, and gamma-aminobutyric acid (GABA) signaling abnormalities. Patients with schizophrenia are usually aware of their surroundings and have a normal Intellectual capacity. It is possible that some of them will acquire cognitive impairment. The condition usually takes a long time to progress and worsen. It is required to use a variety of remedies. The major treatment option is medication, such as chlorpromazine and fluoxetine. G-protein-coupled receptors are the target of many medicines. Furthermore, researchers are attempting to investigate lipid-based self-nanoemulsifying drug delivery system formulations in order to boost pharmaceutical availability. Although medication can help with symptoms like hallucinations, improving cognitive difficulties is more difficult. As a result, psychotherapy is a palliative treatment option. As a result, a combination of medicine and psychological counseling has proven to be the most effective treatment for schizophrenia thus far (F 2021).

2.7.1 Medication

G-protein-coupled receptors are a wide category of membrane protein receptors in eukaryotes that receive messages from their environments and provide information to the organisms. They have the ability to bind substances and initiate a number of intracellular signaling pathways that result in cell changes. GPCRs play an important role in the human body since G-protein-coupled receptors are linked to a variety of disorders, and roughly half of all drugs target G-protein-coupled receptors. As a result, GPCRs are being researched for the treatment of schizophrenia and are showing promise in the field of medical discovery. 5-hydroxytryptamine receptors (5-HT receptors), which are found throughout the nervous system, are promising targets for the development of schizophrenia therapeutics. In the human body, there are 14 distinct 5-HT receptors, 13 of which are G-protein-coupled receptors (McCorvy and Roth 2015). Memory, mood, cognition, and a variety of other functions are all affected by 5-HT receptors and 5-HT. Cognitive function can be blocked by a 5-ht2a receptor (Meltzer and Massey 2011). Antipsychotics such as

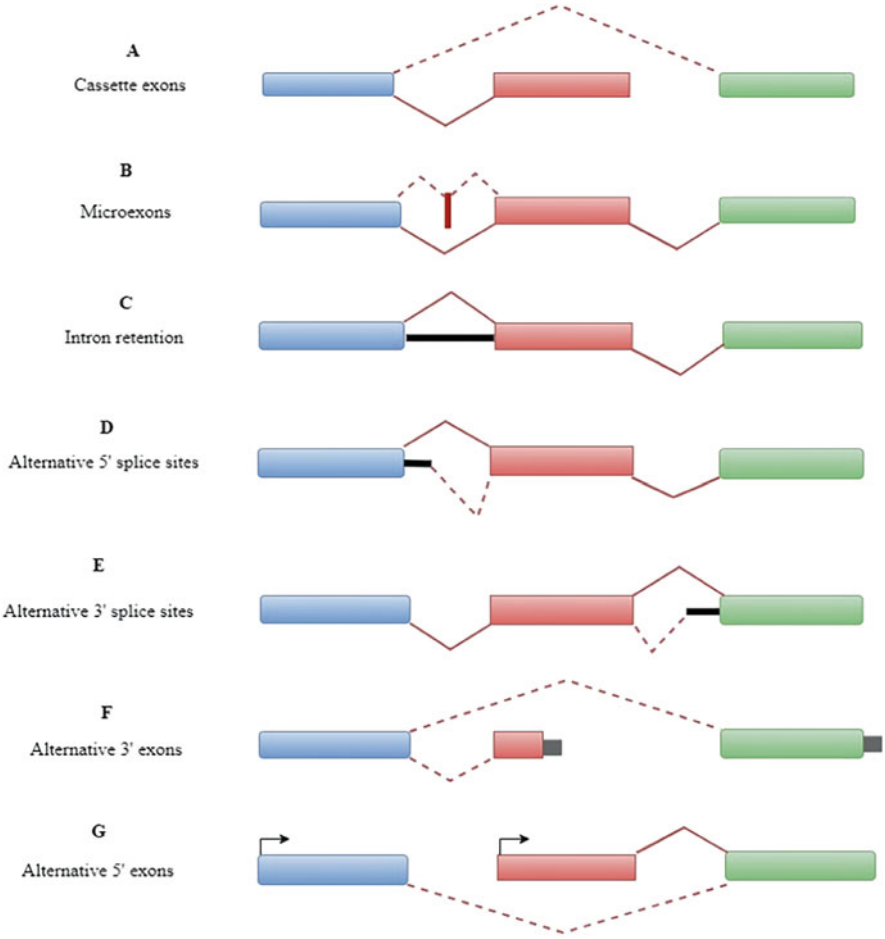

Fig. 2.1 Alternative splicing pattern: Two different splicing options are indicated by the solid and dotted V-shaped lines. (**a**) Cassette exons: The most common pattern of alternative splicing is the inclusion or absence of a cassette exon in the mRNA. (**b**)Microexons are a type of cassette exon that has 3–27 nucleotides and appears to be more common in neuron-specific transcripts. (**c**) Intron retention: the intronic sequence (shown as purple block) is retained in the mature mRNA transcript when intron exclusion is skipped. Exons can be prolonged or shortened by using different combinations of 5′ (donor)/3′ (acceptor) splice sites. (**d**) and (**e**). Alternative 5′/3′ splice sites: exons can be lengthened or shortened by using different combinations of 5′ (donor)/3′ (acceptor) splice sites. (**f**) and (**g**) are two letters that begin with the letter F. Alternative 5′/3′ exons: different transcriptional start or termination locations generate alternative 5′-terminal exons or 3′-terminal exons with alternative polyadenylation sites

clozapine, olanzapine, quetiapine, and others can help individuals with schizophrenia enhance their cognition. These drugs, however, have extrapyramidal side effects (EPS). Stimulation of 5-HT1A receptors or inhibition of 5-HT3, 5-HT6, and 5-HT2A/2C receptors, however, enhances EPS generated by these receptors

(Shimizu et al. 2013). Inhibition of 5-HT1A, 5-HT3, and 5-HT6 receptors, as well as stimulation of 5-HTA receptors, decreases cognitive impairments (Baloch et al. 2019). As a result, medications that target the 5-HT receptor or 5-HT itself make up a significant portion of the existing and future pharma market.

Chlorpromazine is a phenothiazine antipsychotic that can be taken orally. Chlorpromazine hydrochloride levels in the blood and saliva are measured by researchers. CPZ concentrations in saliva are typically 4–50 times greater than those in plasma. The remainder is eventually eliminated by the kidney over a period of 6–9 h. CPZ is used to treat mental and mood problems by reducing excitement, reducing anxiousness, decreasing delusions, and other symptoms, in part by blocking dopamine receptors for emotional thinking and restoring the brain's chemical balance. CPZ also aids patients in thinking clearly and participating in daily activities with friends and family. However, it has a number of side effects, such as dry mouth, impaired vision, and tiredness. When used in big doses for a long time, it might elicit extrapyramidal responses, which is a typical side effect of antipsychotic medicines. CPZ is the main medicine; however, it has a low aqueous solubility. Lipid-based self-nanoemulsifying drug delivery systems (SNEDDS) formulations based on chain triglycerides have been developed in recent years to increase the oral absorption, solubility, and stabilization of CPZ. Because they are lipophilic, incomplete breakdown and deposition of medicines in the gastrointestinal (GI) tract are the main causes of inadequate use. SNEDDS improve the solubility and absorption of lipophilic drugs by increasing surface area and reducing droplet size, which improves the solubilization and permeation of poorly water-soluble drugs like CPZ. Furthermore, SNEDDS has been shown to improve oral bioavailability by increasing lipid fluidity of intestinal cell membranes and reducing cytochrome -P450 metabolism in the intestinal tract (F 2021).

2.7.2 Psychological

Psychotherapies are supplementary treatments for schizophrenia. It is the process of changing a patient's mental activities toward the doctor's intended aim by gradually altering their psychological problems and personalities under the guidance of psychological theory. In schizophrenia, there are numerous types of psychological therapies.

- Involvement of the family: Family intervention, when combined with other evidence-based interventions, may offer a potential path to substantial recovery of function and total avoidance of psychosis. According to the meta-analysis, relapse rates are lowered by 50–60% when compared to standard treatment (McFarlane 2016). Because family members are always active in the process, modifying their attitudes and communicating with the patient at any moment, it is especially beneficial in the early stages of psychiatric diseases. The enhancements

are substantial and long-lasting. As a result, both parents and children must communicate.

- Cognitive behavioral therapy (CBT): CBT is a type of psychotherapy that helps people transform their negative thoughts over a short period of time. It concentrates on current thoughts and actions, identifying and replacing negative ones with more objective and acceptable alternatives. This therapy's power is in its ability to assist the client rebuild their cognitive framework, re-evaluate themselves, rebuild their confidence in themselves, and transform their perspective of themselves as "bad." Cognitive therapy, dialectical behavior therapy (DBT), multimodal therapy, and rational emotive behavior therapy are four different types of mental psychological interventions with different techniques but with the same purpose (REBT). Adult patients with mental disorder between the ages of 18 and 65 who meet DSM-III-R or DSM-IV criteria are randomly assigned to CBT or placebo in trials conducted by the investigators. There is no statistically significant difference between CBT and placebo in terms of weight loss. Comprehensive medical efficiency had a composite ratio of 4.06 (95% CI: 2.78–5.92). The superiority of CBT over placebo is independent of the type of placebo, research year, or duration of treatment (Hofmann and Smits 2008).

2.8 Future Goal and Discussion

The role of alternative splicing in the pathogenesis of a variety of disorders, including autism, amyotrophic lateral sclerosis, and Parkinson's disease, was already recognized, and treatment options based on addressing splicing errors are being examined. Antisense oligonucleotides or CRISPR/Cas9, which can recognize specific RNA splicing regulatory regions, have been widely explored in the clinic (Siva et al. 2014). Such treatments, however, are expected to be more beneficial for Mendelian diseases than for complicated disorders like schizophrenia. Treatment with oligonucleotides or CRISPR/Cas9-based approaches is currently not possible due to the polygenic character of schizophrenia, which necessitates intervention of hundreds or thousands of genes involved in its pathogenesis. As a result, a unique phenomics technique could provide fresh insights into the intricate interaction network between risk genes and clinical features in schizophrenia patients, perhaps uncovering putative hub pathways underpinning endophenotypes in the disease. Although altering alternative splicing in schizophrenia is challenging, a few novel methods may be able to identify the spliced mRNAs or proteins of schizophrenia-associated isoforms. For example, Liu et al. have devised a genetic technique termed "isoTarget" for in vivo isoform functionality characterization, which involves introducing a cassette sequence into an exon to knock out or tag an isoform in a cell-type-specific manner (Liu et al. 2020). Exploring the prospect of using this method to stress or antagonist GPCRs (e.g., DRD2, mGluR3, etc.) to alleviate schizophrenia symptoms while reducing side effects and declining effects after long-term therapy is of significant interest (Patil et al. 2007). Given the splicing

variability of these genes, a greater understanding of the structure and expression patterns of their isoforms in vivo should aid in the development of drugs that target the pharmaceutically active regions without activating other parts of the gene (Marti-Solano et al. 2020). Overall, further focus on altered alternative splicing of schizophrenia risk genes is required for effective translation of genetic discoveries into disease control understanding.

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Chapter 3
Understanding the Chemical Interactions in the Brain of Schizophrenia Patients

Videsha Bansal and Indranath Chatterjee

3.1 Introduction

Human brain is one of the most complex organs in the human body. The outer structure of the brain resembles a walnut, but the internal structure is similar to a complex wired network. The human brain is divided into different parts depending upon their functions. Figure 3.1 is a complete illustration of the human brain and its parts. The human brain is divided into three regions: forebrain, midbrain, and hindbrain. The forebrain comprises cerebral hemispheres, thalami, hypothalamus, and limbic system. The midbrain is the top inch of the brain stem, whereas the hindbrain comprises cerebellum, pons, and medulla (George 2021).

Each region in the human brain is responsible for different functions. Before understanding each region let us understand what a synapse is and how information is transmitted in the brain. All the neurons in the human body are connected to other neurons with the help of dendrites and axon. When we have to perform a task an electrical impulse known as electrochemical synapse is released from a neuron which travels through the axon and at the end of the nerve different chemicals are released in the synaptic cleft (Moulson and Nelson 2008).

These chemicals are known as neurotransmitters which either get absorbed by the receptors on other postsynaptic neurons or pass on the message further. The information in the neurons is passed in the formal of electrical signals and reaches the

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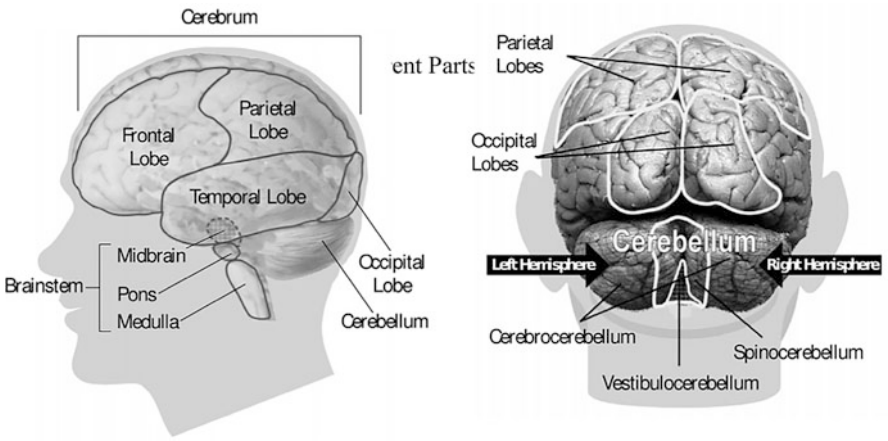

Fig. 3.1 Different parts of the human brain

brain. Neurotransmitters which are released in the synaptic cleft during these synapses are essential for smooth working. Any changes in these neurotransmitters will cause changes in the transferring information from one neuron to the other. If there are significant changes in the level of neurotransmitters in the brain, then a person can suffer from neurodegenerative disorders like schizophrenia and Alzheimer's (Videsha and Chatterjee 2021).

Along with neurotransmitters there are hormones and neuropeptides which help in the construction of our nervous system. To understand the difference between the three of them, let us look at their dictionary meaning (Stevenson 2010):

Neurotransmitters: "A chemical released at the end of nerve to transfer all the electric impulse to another nerve of any other structure" (Stevenson 2010).

Hormones: "A regulating substance produced and transported in organism through blood or sap to stimulate and regulate different tissues" (Stevenson 2010).

Neuropeptides: "A chemical produced in the nervous system which can act as a hormone and neurotransmitter" (Stevenson 2010).

Along with these three chemicals there are enzymes present in the human body which act as a catalyst during biochemical reactions (Videsha and Chatterjee 2021).

All these neurotransmitters and neuropeptides are divided on the basis of their chemical properties. Table 3.1 is a partial list of neurotransmitters and peptides present in the brain along with their chemical properties (Hyman 2005).

Each neurotransmitter is present in different parts of the brain. Therefore, each neurochemical is responsible for different actions. In the next section we will discuss the presence of neurotransmitters in the different parts of the brain and their responsibilities.

Table 3.1 Different neurotransmitters and neuropeptides depending upon their chemical properties (adapted from Hyman 2005)

Chemical properties	Neurotransmitters/peptides
Monoamines and acetylcholine	Acetylcholine Dopamine Norepinephrine Epinephrine Serotonin Histamine
L-amino acids	Glutamate Aspartate Gamma-aminobutyric acid (GABA) Glycine
D-amino acid	D-serine
Purines	Adenosine Adenosine triphosphate (ATP)
Gases	Nitric oxide (NO) Carbon monoxide (CO)
Lipids	Anandamide (endocannabinoid) 2-arachidonoylglycerol (2-AG) (endocannabinoid)
Peptides	Enkephalins (endogenous opioid peptides) Beta-endorphin (endogenous opioid peptide) Dynorphins (endogenous opioid peptides) Substance P Neuropeptide Y (NPY) Peptide YY (PYY) Orexin (also known as hypocretin) Vasopressin Oxytocin Corticotrophin releasing hormone (CRH) Somatostatin Neurotensin Bombesin Galanin Vasoactive intestinal polypeptide (VIP) bradykinin

Source: Hyman (2005)

3.2 Brain: Its Parts

Almost 2500 years ago the understanding of the human brain was very negligible. It is due to years of research we now know that our entire body is mapped in this complex structure. Thus, to understand this complex structure let us divide it into hindbrain, midbrain, and forebrain.

3.2.1 Hindbrain

Hindbrain is the base of the mammalian brain and is located at the back side and comprises three regions: medulla oblongata, pons, and cerebellum. Hindbrain is one of the most important and sensitive areas in the brain (Rhinn and Brand 2001; Jacob et al. 2021). First is the medulla oblongata that controls our involuntary necessary movements like breathing, heartbeats, and swallowing. Next is the pons, again it is responsible for controlling involuntary movements but along with it, pons also controls facial expressions. Pons also helps in gathering information about the body's orientation in the outer space. Finally, it is the cerebellum in the hindbrain.

During a study (Moret et al. 2004) stated presence of different neurotransmitters (serotonin and dopamine) and catecholamines (norepinephrine and epinephrine) in the hindbrain which further extended to the forebrain.

3.2.2 Midbrain

As the name suggests, midbrain is the middle part of the human brain. Midbrain is responsible for controlling various actions like hearing, eye movement, understanding visual information, and even regulating the mood. Midbrain consists of the most important part of the brain, i.e., substantia nigra: "the dopamine producer" (Smidt et al. 2003).

3.2.3 Forebrain

After decades of research, it is finally concluded that it is the forebrain that has changed and developed the most since the mankind existed on the planet Earth. Nerves arising from here travel throughout the brain. It is the forebrain that connects with the cerebral cortex through thalamus (Swanson et al. 2020). Thalamus is responsible for capturing sensory signals and send them to the cerebral cortex for further processing (Min 2010). Cerebral cortex is the sheet that covers our brain. There are millions of neuronal connections in cerebral cortex. It can also be considered as the hub of our creativity, imagination, and consciousness. Neurotransmitters like serotonin, dopamine, noradrenaline, and acetylcholine are present in the cerebral cortex (Jones 1986). Then we have hypothalamus in the forebrain. All our hormones are released from here in our blood streams. Any changes in the hypothalamus can directly cause several health complications. After this we have Amygdala in the forebrain (Swanson et al. 2020). Amygdala is responsible for human emotions. Next we have Hippocampus, it is the memory hub. All our memories are formed in this part of our brain (Ford and Kensinger 2019). Lastly, we have Basal Ganglia to be discussed in the forebrain. After decades of research, it is finally

concluded that it is the basal ganglia which is responsible for controlling our intentional action/movements (Brown 2019). Earlier, it was believed that it is cerebral cortex that is responsible for the same.

It is important to highlight that forebrain and midbrain are connected through basal ganglia and substantia nigra. Dopamine produced in substantia nigra (midbrain) is responsible for regulating the work of basal ganglia (forebrain) (Graybiel 2000).

Other than the above-mentioned parts of the brain it is important to highlight that we can also divide the human brain into two hemispheres, separated by a tract known as corpus callosum which is made up of more than 20 million never fibers. Each hemisphere has four lobes (Jawabri and Sharma 2021):

- Frontal Lobe: Responsible for thinking and planning processes.
- Occipital and Temporal Lobe: Responsible for processing visual and auditory information.
- Parietal Lobe: Responsible for keeping attention and process sensory information.

3.3 Schizophrenia: Its Neurochemistry

According to several relevant literatures schizophrenia is a complex disorder (Videsha and Chatterjee 2021; Zipursky et al. 2013; Reynolds 2008). It is considered as biological and behavioral disorder. However, one thing remains the same, it is a deteriorating disorder (Zipursky et al. 2013). After years of research and contribution in the field of neuroscience, we have various brain images of patients at different stages of schizophrenia. According to the images we have strong evidences that the brain undergoes structural and functional changes as the disorder progress (Chatterjee et al. 2020a, b; Chatterjee and Mittal 2020). The changes in the brain were brought due to the changing neurochemistry in the brain. From a variety of sources, it has been reported that out of all the neurochemicals present in the brain there are four neurotransmitters which have caught the most attention: dopamine, serotonin, glutamate, and GABA (Videsha and Chatterjee 2021; Enkhmaa et al. 2022). Other than these several researchers are also working on other neurotransmitters like norepinephrine, neurotensin, and cholecystokinin (Enkhmaa et al. 2022). Let us now understand the four major neurotransmitters and their role in causing schizophrenia.

3.3.1 Dopamine and Schizophrenia

Dopamine is a monoamine and the only neurotransmitter that behaves as an excitatory and inhibitory neurotransmitter (Sedvall and Farde 1995). It originates in the

neuron of the cell and gets stored in the vesicles. It is produced in the midbrain, i.e., substantia nigra and ventral tegmental. Dopamine is widely spread in the human brain because of four pathways (Videsha and Chatterjee 2021). The following are the four dopaminergic pathways along with their starting and end points:

- Nigrostriatal Pathway: Substantia nigra to basal ganglia.
- Mesolimbic Pathway: Ventral tegmental area to limbic system. This pathway is also known as the reward pathway.
- Mesocortical Pathway: Ventral tegmental area to prefrontal cortex.
- Tuberoinfundibular Pathway—Hypothalamus to anterior pituitary.

Dopamine is responsible to control motor actions, pleasure circuit, and attention memory. Dopamine has five major receptors from D1 to D5. Each receptor is present at different locations and helps in synthesis, firing, and release of dopamine (Davis et al. 1991).

It is understood by now that dopamine plays a vital role in the human brain. Neurological disorders like Parkinson's disease and Schizophrenia are linked to changes in the dopamine level in the different parts of the brain (Birtwistle and Baldwin 1998). The relationship of dopamine and schizophrenia was understood when the dopamine agonist drugs worsen the symptoms of the schizophrenia, whereas the antagonist improved the positive symptoms of schizophrenia. Among all the positive, negative, and cognitive symptoms of schizophrenia, positive symptoms like hallucination, delusion, cognitive impairments, and speech disorganization connect with dopamine level in the human brain during schizophrenia. An increased level of dopamine is associated with schizophrenia. After reading several post-mortem studies, the researchers concluded that the D2 receptors are majorly associated in causing positive symptoms of schizophrenia (Zakzanis and Hansen 1998; Davis et al. 1991; Harrison 2000).

Therefore, Dopamine hypothesis was the first hypothesis proposed for schizophrenia (Brisch et al. 2014). Currently, with the help of different brain imaging technologies like magnetic resonance imaging; positron emission tomography; and functional magnetic resonance imaging (Chatterjee and Mittal 2020; Chatterjee et al. 2020a; Shen et al. 2012) we have a vast database of the anatomical and biological changes in the brain where dopamine is present. According to the present investigations, the dysfunction of dopamine in the prefrontal cortex, substantia nigra, hippocampus, and ventral tegmental regions is associated with various symptoms of schizophrenia (Brisch et al. 2014). Initially dopamine was linked with only the positive symptoms of schizophrenia but now it has been questioned and investigated to connect it with negative and cognitive symptoms. Several researchers have proven a direct connection between D1 and D3 receptors of dopamine with cognitive and negative symptoms of schizophrenia (Shen et al. 2012; Simpson et al. 2014). We can now understand that the relationship of dopamine and schizophrenia still requires further coherence. Theoretical hypothesis upheld with in vivo study is the only solution.

3.3.2 Serotonin and Schizophrenia

Serotonin is scientifically known as 5-hydroxytrptamine or 5-HT is produced from tryptophan and later with the help of monoamine oxidase it breaks into 5-hydroxyindolic acetic acid. It is an inhibitory neurotransmitter and also known as the happy neurotransmitters (Sodhi and Sanders-Bush 2004; Nichols and Nichols 2008). Serotonin spreads through the entire central nervous system. Therefore, the lateral is responsible for controlling heartbeats to proper respiration, from moderating mood to pain sensitivity, from cognitive functioning to regulation of gastro system (Hyman 2005; Reynolds 2008). When a single neurotransmitter is responsible for so many regulations, its role in various neurodegenerative disorders is a must.

The serotonin hypothesis to understand schizophrenia came into frame much later. The relationship between serotonin and hallucination was developed long back when in a research it was observed that the serotonin receptors are blocked after taking lysergic acid diethylamide (LSD) and hallucinations are experienced by the subject (Bennett and Aghajanian 1974). After years of research, various post-mortem reports and scans of schizophrenia patients were studied it was found that there is loss and gain of serotonin receptors 5–HT2A and 5-HT1A, respectively, in different parts of the brain. When talking about serotonin receptors, until now there are seven types of serotonin receptors classified with further subdivision. From receptor 5-HT1 to 5-HT7, 5-HT2 and 5-HT3 are studied in depth to understand schizophrenia (Sodhi and Sanders-Bush 2004; Nichols and Nichols 2008). Regions like striatum and prefrontal cortex are associated with 5-HT2 receptor, whereas regions like hippocampus, amygdala, and cortical are associated with 5-HT3 receptor (Cortes-Altamirano et al. 2018). According to the data from several relevant literature there is some shrinkage seen in the frontal and cingulate cortex (Sodhi and Sanders-Bush 2004). Though this could be collateral damage but what was common was the effective serotonin level in the patients.

Though serotonin can be directly linked with a lot of symptoms of schizophrenia; however, it is unclear whether changes in the serotonin level are the primary or the secondary cause of schizophrenia.

3.3.3 Glutamate and Schizophrenia

Glutamate is one of the excitatory neurotransmitter which is responsible for stimulating the human brain. According to several studies it was observed that all the neurons in the brain get affected when the lateral is injected. The reason behind the same is the widespread glutamate in the brain. Projections of glutamate can be observed in regions like cortical, hippocampal, thalamus, and cortex. The essential role of glutamate is to learn and store the information for a long term, in other words it is also known as long-term potentiation (LTP) (Platt 2007; Greenamyre 1986).

The involvement of glutamate in the schizophrenia model was further understood when drugs like phencyclidine and ketamine were introduced and their effects were observed. The result showed the subjects developed symptoms similar to schizophrenia and the reason was the blockage of glutamate receptor, i.e., n-methyl-D-aspartate (NMDA) (Greenamyre 1986). In the similar line when various post-mortem and brain images studies of schizophrenia patients were brought together it was observed that the regions like temporal cortex, striatal, temporal lobe, hippocampus, and even frontal cortex experienced either elevated or declined level of glutamate (Meador-Woodruff and Healy 2000; Howes et al. 2015). Keeping the roles of these regions considered, it was concluded that any changes in these regions can contribute to the development of cognitive and negative symptoms of schizophrenia. Therefore, this is how glutamate hypothesis was linked to negative and cognitive symptoms of schizophrenia.

However, the study to link glutamate and schizophrenia model still needs more number of post-mortem and brain image studies to back the hypothesis with actual evidences.

3.3.4 GABA and Schizophrenia

Gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter present in the brain. More than 40% of neurons in the brain use GABA as their main neurotransmitter. GABA is synthesized when glutamate undergoes decarboxylation and the acting enzyme is glutamic acid decarboxylase (GAD) (Carlsson et al. 2001; Egerton et al. 2017).

The study of GABA to understand the schizophrenia model is very new. Current available literature strongly focus on the changes in the frontal cortex and hippocampal regions during schizophrenia. These regions are responsible for controlling cognitive functions. These regions experience a deficiency of GAD and other enzymes and this could affect the receptors of glutamate and GABA in long-run (Egerton et al. 2017; Glausier and Lewis 2017).

GABA is currently related to the cognitive symptoms of schizophrenia because when looking for changes in the level of GABA, changes in the prefrontal cortex were observed. However, our knowledge on the relationship between GABA and schizophrenia is very limited. Further focused post-mortem and brain imaging studies are required for any concrete conclusions.

3.3.5 Other Neurotransmitters and Schizophrenia

Other than dopamine, serotonin, glutamate, and GABA scientist have also observed role of other neurotransmitters like norepinephrine, neurotensin, and cholecystokinin to understand the neurochemistry behind schizophrenia (Videsha and Chatterjee

2021; Hyman 2005; Enkhmaa et al. 2022; Sedvall and Farde 1995). The elevated level of these neurotransmitters in the brain of schizophrenia patients is a new research interest.

3.4 Neuroanatomical Changes During Schizophrenia

The journey of schizophrenia starts from a signal episode and then gradually converts into a chronic mental disorder. A person experiences various changes like psychological, behavioral, and even anatomical. The affected levels of neurotransmitters in the brain are responsible for changes in the structure of the brain. The brain consists of three types of tissues gray matter, white matter, and cerebral spinal fluid (Chatterjee et al. 2020b). These can be traced using magnetic resonance imaging. Changes in gray matter, white matter, and cerebral spinal fluid have been observed over the time during schizophrenia. The changes are observed by using various technologies like computed tomography scan, magnetic resonance imaging, positron emission tomography, near-infrared spectroscopy, magnetoencephalogram, electroencephalography, and functional magnetic resonance imaging (Gordon 1999; Gui et al. 2010; Shenton et al. 2022).

There is sufficient literature available to strongly support the changes in the gray and white matter during schizophrenia. Among both, the reduction in the gray matter volume starts first and can be observed in the areas like temporal lobe, prefrontal cortex, and media (Chatterjee et al. 2020b; Bansal and Chatterjee 2022; McCutcheon et al. 2020; Buchanan and Carpenter 1997). The changes in the gray matter in these areas can be associated with the symptoms like poor decision-making and memory issues.

Changes in the white matter are only visible when the disorder has reached a chronic stage. Diffusion tensor imaging method and tractography methods are used to generate brain images (Bansal and Chatterjee 2022). In diffusion tensor imaging technology water is diffused in the neural tissues and fractional anisotropy follows the shape the water takes and integrates the brain images. In schizophrenia changes in the white matter are seen in hippocampus, different parts of the arcuate fasciculus (Buchanan and Carpenter 1997). These regions when looked for roles were responsible for memory and cognitive abilities. Thus, decrease in white matter in the above regions could be linked to the cognitive symptoms of schizophrenia (Bansal and Chatterjee 2022).

In a similar line initially when computed tomography scans were used to study the changes in the brain during schizophrenia, enlarged ventricular were observed. The enlargement increases with time and this was associated with the negative symptoms of schizophrenia (Buchanan and Carpenter 1997).

3.5 Conclusion

Schizophrenia is a complex and chronic disorder. It is hard to manage this disorder and even harder to diagnose it at an early stage. The starting part of the schizophrenia spectrum is often confused with other mental disorders. It is with time the symptoms of schizophrenia progress and schizophrenia is diagnosed. Understanding the neurochemistry behind schizophrenia is important as it helps in pharmacology. Researchers are investigating different areas in schizophrenia, such as, neurobiological studies are performed to understand behavioral changes during schizophrenia. This chapter focuses on the major (mostly investigated) neurological changes in the brain of the patients with schizophrenia. We believe that there is a requirement of more reasonable research on this area to comprehend the entire neurological underpinnings of schizophrenia.

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Chapter 4
A Diagnostic Perspective of Schizophrenia: From Past to Present

Meghna R. Choudhari and Indranath Chatterjee

Schizophrenia is a chronic manic-depressive illness. It is a mental illness characterized by a combination of symptoms such as perceptual misinterpretation, cognitive impairment, and emotional dysfunction. Schizophrenia is a serious mental illness that affects various parts of the brain. “A majority of individuals with schizophrenia have poor insight regarding the fact that they have a psychotic illness, “ says the DSM (Diagnostic and Statistical Manual of Mental Disorders). There are a myriad of symptoms associated with schizophrenia illness, arising from different basis. Hence, it adds slight complexity to its further diagnosis. Symptoms must last 6 months and include at least 1 month of active symptoms for an accurate diagnosis. For a precise diagnosis, several clinical symptoms, including physical, psychiatric, and psychological indicators, must be evaluated. Clinical examination includes a variety of tests to diagnose, including blood tests and medical imaging. Combinatorial methods can be used to make accurate diagnoses. Considering the neurochemical changes in mental disorders, identification of biomarkers in psychiatry is becoming increasingly important in order to facilitate diagnosis. The International Classification of Diseases, eleventh revision, has also adopted standardized criteria (ICD-11) for specific Schizophrenia diagnosis. Various diagnostic tests, such as MRIs, CT scans, and blood tests, are usually performed to assess the patient’s health. With the aid of diagnostic tool, several causative factors in schizophrenia pathophysiology have been identified. It is providing a more promising future for easy and safe diagnosis of schizophrenic patient. To achieve even greater improvements in patient care, psychiatrists and researchers synchronized work contributes to improving and developing modified medicine tools.

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4.1 Introduction

Initially, the term schizophrenia was introduced in the year 1911 but it took 70 years to consider schizophrenia under the category of disease as per the Diagnostic and Statistical Manual of Mental Disorders—third edition (DSM-III) (Tomasik et al. 2012). The term Schizophrenia is derived from the Greek origin, "schizo" (splitting) and "phren" (mind). Swiss psychiatrist Dr. Eugen Bleuler coined the term "Schizophrenia" and in 1911 emphasized the word schizophrenia that, dementia praecox nothing but schizophrenia as it causes differentiation in psychic functions (Ashok et al. 2012).

Mental disorders are usually associated with high risk rate of its occurrence, death, morbidity, and mental instability as per World Health Organization. Schizophrenia is a difficult brain disorder that makes it challenging to distinguish between what is real and what is not, to think clearly, manage emotions, relate to others, and function normally.

L. Bender, Boston psychiatrist and neuropathologist, described schizophrenia as "congenital encephalopathy" (Weinberger and Levitt 2011). It affects human perception by affecting person behavior, thinking, and vision toward the world. Loss of coordination in neurological function leads to a chronic mental health disorder called as Schizophrenia. It is a psychological illness in which people seem like they have lost touch with the fact and are in schizotypal state. The exact cause of schizophrenia is not known, but a blend of causes of schizophrenia is associated with Genes, Environment, or Change in Brain Structures (Sawa and Snyder 2002). It is characterized by symptoms such as delusions, hallucinations, disorganized speech or behavior, and impaired cognitive ability (Chatterjee 2018; Chatterjee and Mittal 2019).

Difficulty can be associated with concentration and memory. Treatment is usually life-long and often involves a combination of medications, psychotherapy, and coordinated specialty care services. Symptoms may persist long when untreated but when treated in a coordinated manner, it can help individuals to carry out normal schedule as a normal and healthy volunteer. As suggested by L. Bende psychiatric disorders are also influenced by environmental factors such as institutional care and non-friendly behavior (Walter et al. 2010). These types of environmental factors affect psychological development and lead to psychological disorder.

Diagnosis is totally dependent on symptoms for the complete estimation of the disorder under its clinical manifestation.

4.2 Clinical Manifestations

Schizophrenia symptoms are categorized mainly into three types,

4.2.1 Positive

Positive symptoms are identified and distinguished from healthy individuals. The symptoms include hallucinations, delusions, and abnormal motor behavior with varying degrees of severity.

4.2.2 Negative

Negative symptoms are associated with high morbidity rate and usually not easily identify. The negative symptoms included avolition, alogia, anhedonia, and diminished emotional expression.

4.2.3 Cognitive

Cognitive refers to conscious intellectual activity (such as reasoning or remembering). And cognitive symptoms involve hampering conscious intellectual activity. These ultimately lead to impairment in the individual's communication skills by affecting speech and responsiveness. Usually impairment is observed in attentiveness, focus of mind, and memory.

Schizophrenia appears in numerous forms. Common types of symptoms include person who hears voices and has extreme fear, or feelings that are unusual and unnatural. Dopamine excessive secretion via secretory neurons is associated with schizophrenia. Drugs that are treating schizophrenia like chlorpromazine, haloperidol, and thiothixene either decrease secretion of dopamine at dopaminergic nerve endings or decrease the effect of dopamine on neurons (Guyton and Hall 2006). Various neurotransmitters such as γ-aminobutyric acid (GABA), glutamate, dopamine, serotonin, and oxytocin contribute the most in causing schizophrenia, among this major role is played by dopamine (Bansal and Chatterjee 2021). These are chemical messengers in the body, used by nervous system to communicate between neurons or from neurons to muscles. Neurotransmitters play an important role in neurodevelopmental disorders. As depicted in (Fig. 4.1) the progression of schizophrenia can be divided into four stages via neurotransmitter interference (Insel and Cuthbert 2010; Bansal and Chatterjee 2021). The figure specifies and represents about clinical symptoms with its diagnosis.

The authors conducted a literature review and discussed the roles of dopamine and glutamate in schizophrenia, including loss of senses, motion, memory, and depression. A low level dopamine amount is usually linked to brain disorders, including schizophrenia (Birtwistle and Baldwin 1998; Bansal and Chatterjee 2021). Though, the patient also experiences physical changes such as weight gain

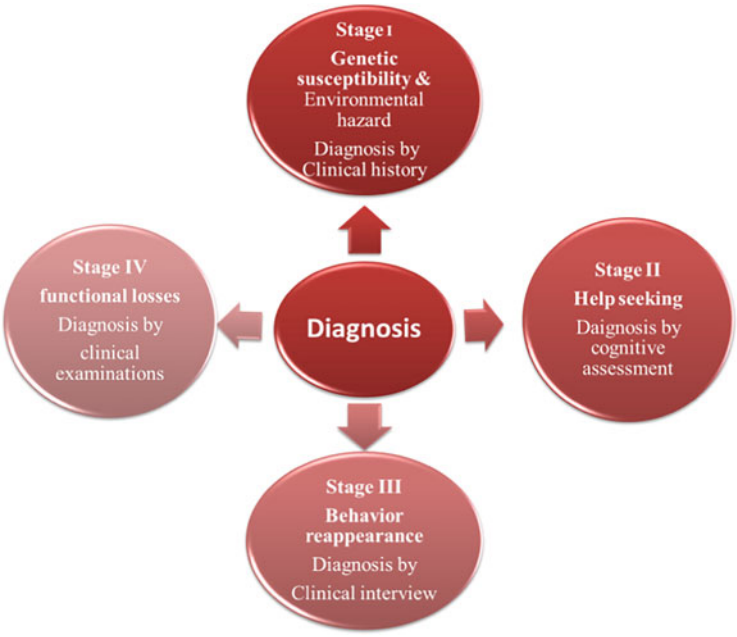

Fig. 4.1 The four stages describing progression of schizophrenia

or loss, diabetes, and suicidal thoughts. The feature of this stage is behavior reappearance, which can be diagnosed through a clinical interview.

4.3 Rationale

Due to the heterogeneity of this mental disorder and the lack of specific effective biomarkers, diagnosing SZ is a difficult problem. Several clinical symptoms, including physical, psychiatric, and psychological indicators, must be assessed for appropriate diagnosis. To diagnose, clinical examination includes a variety of tests, including blood tests and medical imaging. The combinatorial methods can be implemented for efficient diagnosis.

4.4 Diagnosis

For appropriate treatment prior diagnosis of this mental disorder is essential. Schizophrenia is a heterogenic mental illness that requires accurate diagnosis (Shepherd et al. 2012). There are accurate methods available for care and recover of people with schizophrenia. Efficient feature selection techniques result in high classification

accuracy as well as improved identification of affected brain regions (Chatterjee et al. 2019). Hence it is really essential to diagnose the symptoms of schizophrenia as soon as possible for effective care and treatment. The manual DSM-5 elaborates that schizophrenia diagnosis will be based on its symptoms. Clinicians or researchers corelate patients' symptoms with the standard reference book or manual called Diagnostic and Statistical Manual of Mental Disorders (DSM-5) Fifth Edition, published under American Psychiatric Association (APA), where APA is national medical specialty society ensuring access to excellence for psychiatric diagnosis and treatment (APA, DSM-5, 2022). As per the guidelines provided by DSM-5, schizophrenia is diagnosed on the basis of two or more symptoms resembling, hallucinations, delusions, or disorganized speech for minimum 1 month. The other essential symptoms associated are gross disorganization and reduced emotional expression.

Further DSM-5 criteria for diagnosis of schizophrenia comprise:

- Initially, work performance personal care is getting diminished before the onset of symptoms.
- Indications of disturbance lasted for minimum 6 months.
- Depressive or bipolar disorder with psychotic symptoms, as well as schizoaffective disorder, has been weeded out.

The disturbance is not the result of any substance or another medical/health condition.

The International Classification of Diseases, eleventh revision, has also adopted standardized criteria (ICD-11) for specific diagnosis of schizophrenia (First et al. 2015). The International Classification of Diseases and Related Health Problems (ICD) works for maintaining international health reporting and information standard under the ambience of World Health Organization (WHO). ICD-10 diagnostic guidelines, each disorder's diagnostic information is generally divided into three sections. The first section describes the main clinical features as well as "any important but less specific associated features." The second section contains "Diagnostic Guidelines, " which "indicate the number and balance of symptoms usually required before a confident diagnosis can be made." The third section, "Differential Diagnosis, " lists other ICD-10 disorders that must be distinguished from the disorder under consideration.

The inconsistency of the diagnostic details included in the ICD-10 Clinical Descriptions and Diagnostic Guidelines (CDDG), particularly with regard to differential diagnosis, is a significant shortcoming in terms of its usefulness to clinicians.

As a result, ICD-11 Working Groups were tasked with compiling data using standardized template, for providing diagnostic information about the disorders under their purview (known as a "Content Form"). The ICD-11 CDDG is being developed with a uniform structure utilizing the information provided in the Content Forms as basis of the information. This format is effective in producing more reliable clinical judgments in ICD-11 in comparison with ICD-10 and hence is currently being tested in a series of Internet-based field studies using standardized case material, and it will also be tested in clinical settings. For example, the proposed ICD-11 diagnosis of schizophrenia requires the occurrence of at least two of seven

symptoms for at least 1 month. Although statements about the duration of symptoms are frequently included (for example, the diagnostic guidelines for schizophrenia state that "symptoms should have been clearly present for the majority of the time during a period of one month or more").

Guidelines also elaborate about individuals diagnosed with schizophrenia and bipolar disorder have a high prevalence rate of PTSD. Post-traumatic stress disorder (PTSD) is associated with condition that advances as a result of witnessing a highly threatening or horrific event or series of events. Anger, shame, sadness, humiliation, or guilt, including survivor guilt, is the common symptom of PTSD (First et al. 2015). Schizophrenia results in psychosis and is associated with considerable disability and may affect all areas of life including personal, family, social, educational, and occupational functioning. The first-episode psychosis usually appears between age 16 and 30 and is considered as part of diagnosis, where psychosis is the state of mind indulging person to lose contact with reality and affecting his ability to differentiate between fact and fallacy. Such circumstances are classified under psychotic episodes. National Institute of Mental Health (NIMH) reports on U.S data for about 100,000 new cases per year for psychosis. Schizophrenia causes psychosis and it may hinder person's personal, social and professional life as well.

The diagnosis of schizophrenia can be efficiently achieved with the help of studying various parameters comprising of medical history, functional and structural neuroimaging techniques, clinical and physical examination. As per the mental or physical symptoms of the patient, physicians decide medical history and physical examination. Usually various diagnostic tests like MRI or CT scans or blood tests are performed to analyze health condition of the patient. If the physical symptoms are not in accordance, then physician may recommend a psychiatrist or psychologist, healthcare professionals, those are professionally fully trained for further counseling, guidance, diagnosis, and treat mental illnesses where clinical examination comprises blood tests as well as medical imaging (Tomasik et al. 2012).

Schizophrenia basically associated with brain and hence classified as brain disorder, but recently due to its impact on peripheral systems it is also categorized under systemic disorder. The changes are usually associated with cerebrospinal fluid, liver, and skin cells of patients. Blood is such a fluid component of the body that circulates throughout. Hence, blood samples can be easily retrieved without much clinical interventions and considering patients comfort. It is usually carrying molecule those are balancing activity of both central and peripheral purposes. Hence blood may still be a useful component for diagnostic, or certain monitoring purposes as it reflects any change associated with human physiology. Blood of the patient is usually tested for molecular changes in metabolic, immune, and hormonal pathways occurring in schizophrenia patients. These altered molecules lead to high accuracy in diagnosis. Blood samples of schizophrenia patients show considerable changes that are used for diagnosis.

There are certain biomarkers expressed in blood, specific for particular genotype of patient and are responsible for diagnosis and therapeutics (Tomasik et al. 2012). To specify the indication of biological material the term "biomarker" was first introduced in 1973. Biomarkers are biological molecules, genes, or such a molecule

that is associated with any sort of clinical condition to be identified. These molecules are usually found in blood, other body fluids, or tissues of the patient. The Biomarker Definition Working Group, which was funded by the National Institutes of Health (NIH), defined a biomarker as "a characteristic that is objectively measured and evaluated as an indication of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" in 2000.

The concept of biomarkers was further elaborated by Fitzgerald and colleagues in the year 2016 as a molecule having functional variability that acts as a marker or indicator of disease or response to therapy (Fitz Gerald 2016). Recently, science and technology has supreme opportunity to scrutinize inflammation as a potential biomarker in schizophrenia. For a broad range and complete analysis, a set of vivid types of biomarkers may be needed for precise diagnosis along with the application of advance technology such as combination of genomic, proteomic, and immunoassay technologies. Usually, most common biomarker associated with this disorder is inflammatory response. Inflammation can serve as a potential biomarker in schizophrenia as it is a set cascade of reactions to various stimuli, involving activation of immune system, influx of blood, vascularization, and recruitment of mediators such as cytokines, complement activation (Miller and Goldsmith 2019). Inflammation is an indicator of autoimmune disorders and severe infections, enhancing the risk of schizophrenia (Benros et al. 2014). Evidence proves about schizophrenia patients show inflammatory marker as anomalies in blood samples, cerebrospinal fluid (CSF), and central nervous system (CNS), including leukocytes, cytokines, and acute phase reactants (Kirkpatrick and Miller 2013; Mazza et al. 2019). A large number of inflammatory markers, including interferon gamma (IFN-g), IL-1b, IL-1 receptor antagonist (IL-1RA), IL-6, IL-8, IL-10, IL-12, were found to be elevated in a recent meta-analysis of first-episode psychosis (FEP) and chronic individuals with psychosis (Goldsmith et al. 2016).

It has been practically proven that non-steroidal anti-inflammatory drugs (NSAIDs) or other agents with anti-inflammatory effects may help improve mental illness in certain schizophrenia patients (Nitta et al. 2013; Sommer et al. 2014). Hence presence of inflammatory markers in the blood may act as an indication of response to such agents. Considering this finding, it suggests that inflammation may be involved in the pathogenesis of schizophrenia, at least in some patients, and is thus a candidate biomarker for a variety of disorder-related phenomena. The exposure to various sources of infection including prenatal maternal, viral, bacterial infection (Brown et al. 2010) as well as exposure to the parasite *Toxoplasma gondii* acts as a risk factor (Torrey et al. 2007). These risk factors converge toward schizophrenia via common inflammatory response. The risk factors are considered as progenitors of schizophrenia. Detecting inflammatory biomarkers for individuals at clinical high risk (CHR) for psychosis is critical, because they may serve as important diagnostic, prognostic, and theranostic predictors. Individuals with CHR are a diverse group (Fusar-Poli et al. 2017). As per the estimation made within 2 years, approximately 20% of CHR individuals convert to a first-episode psychosis (FEP). Finally, understanding the role of inflammatory biomarkers in treatment response, as well as their relationship with specific psychotic symptoms, may

provide important data to support a putative causal role for the immune system in psychosis.

A recent meta-analysis provided the first systematic evidence for changes in inflammatory markers in CHR patients versus healthy controls (HC) (Park and Miller 2019). In seven studies that looked at 10 cytokines and the acute phase reactant, CRP or "C-reactive protein," IL-6 was found to be significantly elevated and IL-1b was found to be significantly decreased in CHR patients compared to healthy controls (Delaney et al. 2019; Focking et al. 2016).

Meta-analysis estimated risk associated with schizophrenia enhances due to elevated level of inflammatory markers like in maternal blood circulation CRP, IL-8, and IL-10 during pregnancy (Zhang et al. 2018). It is especially common in medicine and epidemiology, where it is frequently used to combine results from observational studies, guide policy decisions, and help determine the efficacy of medical interventions. Meta-analysis focuses on, reviewing and quantitative analysis and synthesis of raw data, Gene V Glass is a statistician and social scientist from the USA. He introduced the term "meta-analysis" and initiated using it in his presidential address to the American Educational Research Association in April 1976 in San Francisco.

For instance, a meta-analysis of 40 published data was performed to determine the magnitude and direction of the relationship, or effect size, between insight and symptom domains in schizophrenia, as well as moderator variables associated with the variations in effect sizes across studies. According to the discoveries of this meta-analysis, in schizophrenia, the relationships between insight and symptom domains are significant but modest. To summarize, the findings revealed a negative relationship between insight and global, positive, and negative symptomatology, implying that as global, positive, and negative symptoms increased, so did the degree of insight. In schizophrenia, there was an affirmative correlation between insight and depressive symptoms, implying that as the level of insight increased, so did the level of depressive symptoms. The findings of this meta-analysis have far-reaching implications for future research. The relationship between insight and symptoms has been studied extensively, and meta-analytic results indicate that, while statistically significant, these relationships are only moderate at best (Mintz et al. 2003). Certain comorbid infections are linked to schizophrenia and have a higher prevalence. Schizophrenia is also linked to an increased risk of death from infectious diseases such as pneumonia and influenza (Saha et al. 2007). A variety of different infectious agents have been linked to an increased risk of schizophrenia (Brown and Derkits 2010).

Lower urinary tract infections (UTIs) were found to be more common in schizophrenia patients, particularly during episodes of illness exacerbation, and this may be a recurring phenomenon. Recurrent urinary tract infections have also been reported in acute psychosis or during an acute relapse of schizophrenia (Laney et al. 2015; Miller et al. 2013). In a meta-analysis, it was discovered a 1.7-fold increase in the jeopardy of positive *T. gondii* IgM antibodies—a marker of acute/recent exposure or reinfection—in patients with acute psychosis (especially exacerbations of chronic schizophrenia) compared to controls. Most previous research has concentrated on

T. gondii IgG Immunoglobulins, which are a marker of lifetime toxoplasmosis exposure, whereas IgM antibodies are a marker of acute/recent infection. *Toxoplasma gondii (T. gondii)* exposure is a strong risk factor for schizophrenia.

In this study by Monroe et al. (2015), meta-analysis was carried out to find relationship between *T. gondii* IgM antibodies and acute psychosis in schizophrenia to see if infections were involved with relapse in schizophrenia, also increased seroprevalence of *T. gondii*, antibodies were found in patients with acute psychosis who were compared to controls. An augmented seroprevalence of *T. gondii* IgM in patients with acute psychosis adds to and expands on previous findings, implying that infections may play a role in the etiopathophysiology of relapse in some patients with schizophrenia (Monroe et al. 2015). In each study, data were extracted for sample size and the number of subjects seropositive for *T. gondii* IgM antibodies for acute psychosis and controls. Hence the data is relevant for the serodiagnosis that comprises diagnosis based on the study of blood sera in relevance with the meta-analysis, thus making diagnosis and coprevalence of other symptomatic infection with schizophrenia. Several other studies have discovered an increased prevalence of active viral and chlamydial infections in hospitalized patients suffering from acute psychosis (Ahokas et al. 1987). From the analysis of Fellerhoff et al. the data showed 9.4-fold increased risk of chlamydial infection in 72 schizophrenia patients compared to 225 controls (Fellerhoff et al. 2007). The current study's findings suggest a link between *T. gondii*, C. trachomatis infection, and schizophrenia. More research is needed in the future to determine the relationship between the two types of infection and schizophrenia (Park et al. 2012).

Past and ongoing neuroimaging studies have found morphological brain alterations in schizophrenia, and magnetic resonance spectroscopy (MRS) studies have revealed about changes in living brain chemistry and molecular alterations in schizophrenia. For the purpose of diagnosis standardized tools and techniques are described as follows.

4.5 Magnetic Resonance Spectroscopy (MRS) for Schizophrenia

Ackerman et al. initiated in vivo MRS, being a non-invasive technique that provides useful information about brain chemistry (Ackerman et al. 1980). The most commonly used cores for in vivo studies comprises ^{31}P and 'H. ^{31}PMRS is particularly well suited for studying neurodevelopmental aspects of schizophrenia pathophysiology by measuring phosphorus-containing metabolites, where the stable isotope of phosphorus is phosphorus-31 for the study. ^{31}P MRS can be used in the brain as part of a clinical protocol to provide accurate measurements of crucial metabolites (Novak et al. 2014). There is mounting evidence that schizophrenia is associated with abnormalities in the composition and metabolism of cell membrane phospholipids (PLs) in the brain. In schizophrenia, ^{31}P MRS was used to measure the

metabolic precursors and degradation products of PL metabolism (Komoroski et al. 2008). Metabolite ratios were quantified precisely enough to detect significant differences between brain regions. Using high-resolution (Fusar-Poli et al. 2017) P NMR spectroscopy, the absolute concentrations of the individual PL metabolites phosphocholine (pc), glycerophosphocholine (gpc), phosphoethanolamine (pe), and glycerophosphoethanolamine tissue from frontal, temporal, and occipital cortex of brain for schizophrenia were determined. Pettegrew et al. discovered reduced PMEs (phosphomonoester) and elevated (phosphodiester) PDEs in the dorsal prefrontal cortex of drug-naive schizophrenics in their groundbreaking study (Pettegrew et al. 1991). Since then, most studies have found lower PMEs and higher PDEs in first-episode schizophrenia. PMEs are reduced in chronic, schizophrenia, but the results for PDEs are differing.

Tissue samples are extracted using a modified Bligh–Dyer method (Bligh and Dyer 1959). In this method brain tissue is given chemical treatment followed by incubation period and thawing. Following subsequent steps, then aqueous layer is used for NMR analysis (Komoroski et al. 2008). For the study, PL metabolites in the three brain regions for the three complete subject groups were considered. The results for the relevant metabolite ratios pe/gpe and pc/gpc, summed PMEs (pe + pc = "PME"), and summed phosphodiesters (gpe + gpc = "PDE") are also provided. These sum-up values approximate the quantities measured in the in vivo ^{31}P MR spectra of the brain. The metabolite concentrations found here are comparable to those found in vivo using (Fusar-Poli et al. 2017) P MRS (Jensen et al. 2002). Although higher gpc is detected in the occipital cortex, the control region, as well as the frontal and temporal cortex, it eventually confirms in vivo results of increased PDEs in schizophrenia. The study considering MRI data has been thoroughly investigated by Chatterjee et al. (2020) about changes in the volume of gray matter as the characteristics of schizophrenia patients in comparison to healthy controls. The findings show a significant decrease in gray matter volume in schizophrenia patients' brains, most notably in the inferior frontal gyrus, superior temporal gyrus, middle occipital gyrus, and insula. This study added a boon to the way for further research into the underlying neurobiology of the schizophrenic brain contributing to clinical interventions (Chatterjee et al. 2020). fMRI scans use the same fundamental atomic physics principles as MRI scans; however, MRI scans image anatomical structure and fMRI scans image metabolic function. As a result, the images produced by MRI scans are three-dimensional representations of anatomic structure. Another tool used for neuroimaging is functional magnetic resonance imaging (fMRI). The most widely used technique for studying the functional activation patterns of the brain is functional magnetic resonance imaging (fMRI). The fMRI data is four-dimensional, consisting of three-dimensional brain images collected over time (Chatterjee 2018).

4.6 Molecular Pathology of Schizophrenia

Pathology is the study of the causes and consequences of disease or injury. Generally, the term pathology implies the study of diseases. It encompasses a wide range of biological research fields and medical disciplines.

There are three major concepts in context to development of schizophrenia. According to the neurochemical abnormality, the psychiatric manifestations of the disease are caused by an imbalance of dopamine, serotonin, glutamate, and GABA. Evidence indicated that the number of dopamine receptors are increased in a brain proportion. As demonstrated (possibly two-thirds) of patients with schizophrenia utilizing receptor assay techniques (Owen et al. 1978; Lee et al. 1978).

Burt et al. conducted a study in rat to assess dopamine receptor supersensitivity, using the haloperidol-binding technique (Burt et al. 1977). In later studies, haloperidol was replaced with Spiroperidol 20 (due to its advantages) as a dopamine receptor assay and linked changes in receptor sensitivity in human post-mortem brain to changes in dopamine concentrations and dopamine turnover measured as concentrations of the metabolites homovanillic acid (H.V.A.) and dihydroxyphenylacetic acid (DOPAC). Dopamine turnover was not increased in schizophrenic patients, but there was a significant increase in postsynaptic receptor sensitivity as measured by the spiroperidol-binding technique. Dopamine neuron hyperactivity may be the primary disturbance in some schizophrenic illnesses.

Because of their opposing effects on the adenylate cyclase system, two distinct subtypes of dopamine (DA) receptors have been identified. Kebabian and Calne proposed that DA receptors linked to adenylate cyclase stimulation be classified as D_1 receptors, while DA receptors that do not increase enzymatic activity be classified as D_2 receptors (Kebabian and Calne 1979). When assays are performed in the presence of guanine nucleotides, the apparent affinity of agonists for D_2 receptors labeled with [3H] spiroperidol ([3H]SPD) is reduced. This finding implies that D_2 receptors regulate adenylate cyclase via a guanine nucleotide-binding protein. Direct evidence of D_2 receptor inhibition of adenylate cyclase has been obtained in studies with pituitary and striatal tissue from rats. D1 and D2 receptor interplay may be important in schizophrenia and the development of novel antipsychotic drugs (APDs) to treat all symptoms of schizophrenia.

4.7 Neuroimaging in Schizophrenia: Advancement in Technique

Schizophrenia, once thought to be a psychological disorder with no organic brain substrate, has been the subject of intense neuroimaging research. Where Neuroimaging process of creating images of the structure or activity of the brain or other parts of the nervous system using techniques such as magnetic resonance imaging or computerized tomography. Magnetic resonance imaging, magnetic resonance

spectroscopy, diffusion tensor imaging, functional magnetic resonance imaging, and radionuclide imaging are examples of neuroimaging techniques currently in use (Yildirim and Tureli 2015). Neuroimaging techniques have emerged as critical tools for investigating brain dysfunctions that underpin psychiatric disorders.

Functional neuroimaging techniques revealed that schizophrenia patients have diffuse functional disorders in various areas and networks of the brain is known as the default mode network. Neuroimaging techniques have contributed promptly to the scientific community's understanding of the pathophysiology of schizophrenia.

Physicians recently geared up diagnosis with the help of medical imaging field, computer aided diagnosis systems (CADS) is the computer-based system using advanced image processing and artificial intelligence (AI) techniques that helps in rapid decisions with automation and accurate diagnosis.

Methods applied for accurate diagnosis are categorized under Functional and structural neuroimaging techniques (McGuire et al. 2008; Aine et al. 2017). The magnetic resonance imaging (MRI) is a widespread technique revealing structural/functional brain abnormalities associated with schizophrenia. Both structural/functional brain abnormalities can be explored with the help of its three-dimensional resolution. Magnetic resonance imaging (MRI) is a medically associated non-invasive neuroimaging technique that is associated with detailed imaging of the organs and tissues of the body. The magnetic field and computer-generated radio waves create three-dimensional anatomical images. MRI structural neuroimaging focuses on visualizing abnormalities in context to white matter (WM), gray matter (GM), and CSF tissues of the brain. (Diwadkar et al. 2011; Varshney et al. 2016).

To establish an accurate diagnosis of SZ, several artificial intelligence (AI) tools are combined with modern image/signal processing methodologies.

4.8 Computed Tomography (CT Scan)Analysis

It is a type of tomography in which a computer directs the movement of the X-ray source and detectors, analyses the data, and generates the image. During CT scan (Fig. 4.2) the X-ray beam moves around the body circularly, during a brain CT scan, allowing for many different views of the brain.

Ventricular enlargement and cortical atrophy are found in some schizophrenic patients. Ventriculomegaly has been found associated with advanced age, impairment of cognitive abilities, poor treatment response, and the prevalence of unpleasant symptoms (Smith et al. 1997). Since the presence of cortical atrophy and/or ventricular enlargement is typically considered to be pathologic signs (Bigler 1987). The first computerized tomography (CT) study of schizophrenic patients was published in 1976 by Johnstone, Crow, Frith, Stevens, and Kreel. Astonishingly, they discovered a higher incidence of ventricular enlargement and cerebral atrophy in their schizophrenic subjects (Bigler 1987).

Study conducted by Malla et al., regarding brain CT scan on 114 patients, had been diagnosed with first-episode schizophrenia. The Computed Tomographic

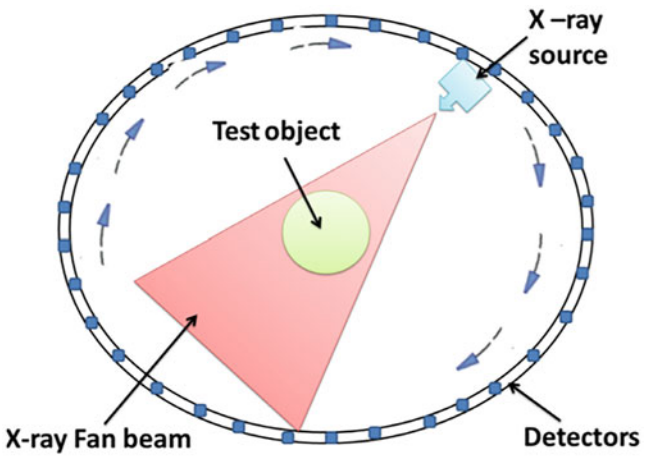

Fig. 4.2 Principle of computed tomography

Rating Scale for Schizophrenia was used to obtain ratings on sulcal and ventricular enlargement, as well as the sylvian fissure. CT ratings were also compared to those of a group of chronic schizophrenia patients. Results obtained showed patients with a first episode of schizophrenic psychosis had morphological changes similar to those seen in chronic schizophrenia. Such changes are most likely influenced by age rather than sex, clinical symptoms, or duration of untreated psychosis (Malla et al. 2002).

4.8.1 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is a medical imaging technique that is non-invasive. It creates detailed images of patient's organs and tissues by using a magnetic field and computer-generated radio waves. The working principle of MRI is based on, hydrogen atoms experience a small torque when exposed to a magnetic field. It rotates at a specific resonant frequency. This external stimulus causes the hydrogen atom to transition from equilibrium to an excited state. When the stimulus is removed, the excited state spontaneously decays back to equilibrium with time, and the nucleus emits an energy that can be detected with the MRI unit's receiver coils and converted into gray-scale pixelated images via complex mathematical transformations (Texada and Singh 2010).

The contrast resolution of magnetic resonance imaging (MRI) is four times that of CT.

The process in MRI is different; it is based on a complex interplay of diverse tissue reactions to applied magnetic fields, whereas CT is based on differential X-ray beam attenuation.

A study reported for schizophrenia, during first episode there is a 4% decrease in gray matter volume, whereas white matter is unaffected. From the initial strike, this structural shift was obvious (Lieberman et al. 2001; Kasai et al. 2003). Auditory hallucinations have been linked to volume loss in the superior temporal gyrus, while negative symptoms have been linked to volume loss in the prefrontal lobe (Szeszko et al. 2000). In cases of first-time psychosis, MRI is recommended, especially if there are unusual symptoms, rapid or atypical development of psychosis, dementia, and the presence of focal neurologic deficits or symptoms. The most consistent finding from computed tomography (CT) and magnetic resonance imaging (MRI) studies to date has been slightly enlarged lateral ventricles, which may be indicative of volumetric reduction of gray matter in the frontal and temporal regions, though the amygdala and hippocampal regions have also been implicated (Chua and McKenna 1995; Malla et al. 2002).

If the physicians do not find a physical cause for the suspected symptoms of SZ, they may refer the patient to a psychiatrist, psychologist, or other related experts. The main psychological assessment focuses on clinical interviews based on diagnostic and statistical manual (DSM-IV) of mental disorders conducted by clinical psychiatrists to diagnose patients with SZ (Maj 1998).

4.9 Psychometric Analysis

Psychological testing might also be used by physician to dig deeper into the symptoms of schizophrenia. These tests may involve the following:

Cognitive testing, personality evaluations, the Rorschach (inkblot) test are the example of open-ended or projective testing. For a psychological examination, information can also be acquired by the therapist in questionnaire format from family or friends including parameters such as:

Behavioral changes in the patient, previous social functioning level, family health history including clinical history of family in context to mental illness. Medical and psychological issues in the past, medications. Psychiatrists and other medical professionals were preferred in the past. Clinician can also discriminate in patient if symptoms are caused by schizophrenia or are the effect of any medications. Substances like marijuana can cause psychotic symptoms. Certain toxicology test can be used to evaluate chemical substances contributing to psychotic symptoms. Symptoms can occur when inebriated as well as during withdrawal.

For the diagnostic interview of people at ultrahigh risk (UHR) of psychosis, several psychometric tests are available. The development of psychometric tools to identify subjects at ultrahigh clinical risk (UHR) of psychosis in the future has enabled preventative screening using diagnosis with interventions. Jackson and McGorry were the first to initiate reliability studies in 1991, using a semi-structured interview to psychometrically assess first-episode subjects in order to determine the presence of prodromal signs and symptoms (Jackson et al. 1994). As per the findings, Yung and colleagues established the first clinical service for UHR

individuals in 1995 and developed the first UHR psychometric instrument (Yung et al. 1996). The Royal Park Multidiagnostic Instrument for Psychosis (RPMIP) is a validity-oriented assessment procedure for acute psychotic episodes that uses serial interviews and multiple information sources to build a clinical database.

4.9.1 Cognitive Analysis

There is evidence supporting use of cognitive behavior study to control schizophrenia. Extensive evidences are in accordance that core feature of schizophrenia is cognitive impairment; assessing cognitive function is a vital step in patient's analysis with schizophrenia. Schizophrenia reflects into cognitive deficits as well as positive, negative, and disorganized group of symptoms.

According to the finding, (Schaefer et al. 2013) schizophrenia is associated with impairment cognitive performance domains is evident from hundreds of studies and thousands of individuals. A instrument called, The Brief Assessment of Cognition in Schizophrenia (BACS) helps in quick assessing the aspects of cognition to be most impaired and showed correlation with outcome in schizophrenia patients. The time required for the testing with the BACS is approximately 30 min with minimal extra time for scoring and training demands (Kaneda and Keefe 2015). Dr. Kaneda attempted to create an abbreviated version of the BACS (Abbreviated BACS, A-BACS) to make it more convenient for clinical work, based on the initial Japanese BACS. Hence is in charge of creating the Japanese version of the BACS. Dr. Keefe conducts BACS testing battery and the MATRICS battery (BACS Symbol Coding).

The BACS was found to be sensitive to cognitive impairment in schizophrenia patients as a standard battery of tests that took over 2 h to administer. In both patients ($r = 0.76$) and healthy controls ($r = 0.90$), the BACS composite scores were strongly in accordance with the standard battery composite scores. These psychometric properties make the BACS a promising tool for analyzing cognition in patients with schizophrenia regularly (Keefea et al. 2004).

Reviews highlight large deficits in cognitive behavior, the areas of verbal episodic memory (Heinrichs and Zakzanis 1998; Reichenberg and Harvey 2007), executive functioning (Reichenberg and Harvey 2007), or processing speed (Dickinson et al. 2007), the most consistent finding across studies has been an overall, generalized impairment across neuropsychological measures that persists in every clinical state and across patients' lifetimes. Another study conducted by Hidese et al. suggested about Japanese version of the BACS (BACS-J) measures, the working memory and motor speed scores are associated with several structural alterations in the brains of patients with schizophrenia (Hidese et al. 2017).

4.9.2 Clinical Observations and Analysis

In healthcare, clinical observations refer to the act of measuring, questioning, evaluating, or otherwise observing a patient or a specimen from a patient; making a clinical judgment. Collecting data based on result, answer, judgment, or knowledge gained from monitoring a patient or a specimen procured from a patient is collectively referred to as clinical observations. An assessment was conducted using neuropsychological screening instrument and two everyday behavior observation scales in describing cognitive and functional capacity in patients with multiepisode schizophrenia (Bagge et al. 2017). The nature and number of symptoms, as well as functional capacity disturbances, vary throughout the course of schizophrenia in the patient (Tandon et al. 2009).

Patients selected in the study were within the age range of 18–65 years, International Classification of Diseases 10 F20.0–F20.9 (schizophrenia) or F25.0–F25.9 (schizoaffective disorder) diagnoses in the last 5 years. Exclusion criteria included acute serious psychotic episodes or physical illness, alcohol or drug abuse in the year preceding the study, a diagnosed cerebral disorder at the time of admission to the unit, and a limited ability to communicate (Bagge et al. 2017).

The Barrow Neurological Institute psychologist scored the Screen for Higher Cerebral Functions (BNIS); nursing staff scored the Frontal Systems Behavior Scale (FrSBe) Family Version and the Functional Independence Measure (FIM) V.4.0. The findings from this study suggest that the BNIS, FrSBe, and FIM may be useful assessment tools in clinical work with middle-aged patients who have multiple episode schizophrenia spectrum disorders and require comprehensive care. The findings indicate that the investigated group has significant cognitive impairment, executive dysfunction, and functional disability. Executive dysfunction has been linked to frontal lobe dysfunction. The Barrow Neurological Institute Screen for Higher Cerebral Functions (BNIS) situated in Phoenix, Arizona, USA is a world leader in the treatment, research, and education of brain and spinal diseases, conditions, and injuries. It is led by Barrow President and CEO Michael T. Lawton, MD, one of the world's leading neurosurgeons. Clinical Trial Numbers for Barrow used to test stroke survivors who are young and middle - aged for cognitive dysfunction. The BNIS and the Mini-Mental State Examination (MMSE) is considered for the patients (Redfors et al. 2014).

4.10 Psychological

Suicidal behavior is more common in people with schizophrenia, although there is little understanding of the psychological factors that add to this vulnerability. The biopsychosocial "Cry of Pain" paradigm offers a comprehensive framework for understanding suicidal behavior. However, the model's efficacy in connection to suicide in schizophrenia has yet to be investigated (Bolton et al. 2007). The Overlap

model, for example, considers the influence of psychosocial milieu (primarily social support), biological vulnerability, psychiatric disorder, personality factors, and family history; the Three Elements model, which includes risk factors, predisposing factors, potentiating factors, and suicidal threshold; and the Cubic model, which takes into account the "press" of external events, the "pain" of unmet psychological needs, and the "perturbation" of the state of mind, Suicide as a Career within the context of a person's life; and the Suicide Trajectory model, which focuses on the combination of biological, psychological, cognitive, and environmental elements that trigger the "last straw" of suicide thoughts and deeds (Sangadah and Kartawidjaja 2020).

Suicidal ideation and preparation, it has been believed, are key steps that lead to a self-harm attempt that may result in death, with previous unsuccessful suicide attempts increasing the probability of further successful suicide attempts (Kontaxakis et al. 2004).

A large body of research has found a variety of socio-demographic and clinical characteristics that are associated with an elevated risk of suicide in the general population and also apply to schizophrenia. Being a man, being younger, being socially isolated, misusing substances, being unhappy and/or feeling hopeless, having attempted suicide before, and having a family history of suicide are all risk factors (Caldwell and Gottesman 1992).

Not only does a theoretical approach help us comprehend suicidal behavior in schizophrenia, but it also helps us grasp the putative underlying causes of suicide in general. There are three broad theoretical views to consider. To begin with, there may be central elements of suicidal behavior that are shared by a variety of mental illnesses, implying a single transdiagnostic, albeit multi-factorial, causative process that acts across a variety of disorders. Second, there may be characteristics that are unique to individual diagnoses, reflecting non-uniform mechanisms underpinning suicidal behavior, such as acting on voices that demand suicide. Third, and in contrast to the previous scenario, suicidal behavior could be linked to a cluster of symptoms linked to a single disease. Depression is a likely contender because it is typically comorbid with schizophrenia, with some estimates claiming that 50% of those with psychotic symptoms also had one or more major depressive episodes (An Der Heiden et al. 2005).

It is also crucial to keep in mind that any of the three speculative scenarios listed above could apply. A fourth option is that there are factors that are part of a general transdiagnostic mechanism in that they apply to a variety of psychiatric diseases but are modulated by aspects of a specific disorder. To give a specific example, stress may be a generally predictor of suicide risk, but it is exacerbated by specific characteristics of psychosis.

4.10.1 Stressors Presence

The first section of the "Cry of Pain" model argues that people with schizophrenia are more probable than the common population to commit suicide as a result of an increased number of stressful events due to the illness's burden and enhanced sensitivity to stress.

4.10.2 Presence of External Stress

Significant losses appear to precede suicide in people with schizophrenia, but not as much as in the general population (Heilä et al. 1999).

4.10.3 Presence of Internal Stress

Because of increased emotions of entrapment, helplessness, and melancholy, stressors linked with internal issues related to psychosis may plausibly lead to suicide behavior in schizophrenia (Beck-Sander et al. 1997).

4.10.4 Stressors Appraisal

The importance of external and internal stressors is assessed as suggestive of defeat or rejection, in accordance with the second component of the Cry of Pain model.

4.10.5 External Stress Appraisal

Birchwood and colleagues' research backs up this theory, claiming that particular sorts of sickness assessments, such as loss (for example, status and goals), threat, shame, or imprisonment, might lead to depression (Birchwood et al. 1993).

4.10.6 Internal Stress Appraisal

Hallucinations and delusions were found to be positively linked with self-reports of entrapment, according to the Cry of Pain model. The voices were perceived as critical of the individual and as signaling poor social value, which had negative

impacts on auditory hallucinations. Surprisingly, depression was a byproduct of these unfavorable evaluations rather than being the fundamental cause (Birchwood et al. 1993).

4.10.7 Impairment of Cognitive Processes and Cognitive Biases

According to the Cry of Pain model, reasoning and problem-solving biases may be particularly essential components of suicide behavior because they restrict the invention and implementation of constructive alternatives. Autobiographical memory biases are thought to play a vital role in suicidal thoughts and behaviors because they prevent certain types of experiences (especially positive experiences) from being encoded and preventing individuals from updating schema, potentially blocking access to effective problem-solving incidents (Bentall et al. 2001).

4.10.8 Reasons and Problem-Solving of Biases

Suicidal people, including those who have delusions, have been shown to have suboptimal reasoning processes, which include accumulating less data before making decisions (i.e., "jumping to conclusions"), excessive responses (i.e., " dualistic thinking"), and metacognitive or belief inflexibility. Suicidal people have been demonstrated to be bad at addressing problems, especially interpersonal ones. In a battery of tests designed to examine the development and appraisal of solutions during social problem-solving, people diagnosed with schizophrenia were compared to those diagnosed with bipolar illness and a nonpsychiatric control group. When compared to nonpsychiatric controls, those with bipolar illness and schizophrenia did worse on all measures of social problem-solving (Garety et al. 2005).

4.10.9 Related to Memory and Memory Retrieval Deficiencies

Working memory was found to be the foundation for these cognitive elements, and executive processes in working memory integrated the representation of social information essential for adequate and acceptable social interactions. Working memory directs expectations regarding cognitive and social information while also facilitating automatic processing, freeing up cognitive resources for other tasks. As a result, deficits in executive working memory processes are likely to increase the demands of effortful processing and decrease social problem-solving capacity (Barch 2006).

4.11 Questionnaire

4.11.1 Positive and Negative Symptoms Questionnaire

When considering patient outcomes, it is critical to assess both positive and negative symptoms. The state of a patient's premorbid functioning might signal both negative and positive symptoms. Andreasen proposed a link between negative feelings and premorbid functioning in 1982. Addington and Addington investigated this concept further (1993). Males exhibited much worse premorbid functioning than females, according to the study. Furthermore, in contrast to individuals with negative symptoms, those with positive symptoms experienced a significant reduction in symptomatology with time, according to a longitudinal research. Furthermore, there was a substantial difference in the amount of time spent in therapy between individuals who had unpleasant symptoms and those who did not. Brain imaging techniques, both functional and structural, have become an important aspect in evaluating positive and negative symptoms. There is a lot of contradictory information out there about how effective these tactics are. It implies that, brain imaging, focused on the temporal and frontal lobes, can reveal anatomical brain defects particular to schizophrenia patients. Deficits in semantic, episodic, and short-term memory, impulsivity, and other cognitive domains have been linked to the loss of brain matter in these locations. Large ventricles are a typical feature in schizophrenia patients and can help explain cognitive problems. Andreasen explained in 1985 that functional and structural imaging modalities may not reflect common features characterized by positive symptoms. The ventricles of the participants were found to be somewhat smaller. However, there appeared to be common brain abnormalities stated in the previous article when examining negative symptoms, implying that negative symptoms are linked to left hemisphere abnormalities. While imaging techniques have some advantages, they are not always practicable in outpatient or inpatient clinical settings. While the visual impact can reassure patients and aid in the detection of other neurological irregularities, it may not be a cost-effective measure due to insurance fees, time constraints, and a lack of skilled workers when it comes to patient load. Some practices may request MRI and CT scans to rule out any brain damage or to look for organic disorders that could be the cause of underlying psychosis, but this is not always necessary. Functional imaging was only determined to be "relevant pathology" in 11% of MRIs, showing that it is not the end-all source for those seeking a diagnosis. Patients may then be referred to certified professionals who will assess their current mental abilities (Sangadah and Kartawidjaja 2020).

4.12 Conclusion and Scope of Future Work

Detailed data on the severity and distribution of psychosis symptoms across schizophrenia spectrum subdiagnoses, as well as brain scanning and pharmacological data, may help to improve comprehension of the nature of cognitive impairment and problems with daily functioning in patients with multiple episode schizophrenia and complex care needs. Future medical research is expected to pave the way for a more promising future in schizophrenia treatment and, theoretically, cure. For more improvements in patient care, the synchronizing role of psychiatrists and researchers must be performed for the improvement and development of modified medicine tools. It will undoubtedly contribute to a brighter future for schizophrenia patients.

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Chapter 5
Is It Schizophrenia or Not? Different Biological Characterization

Videsha Bansal

5.1 Introduction

Since 1800, schizophrenia (SZD) has been a topic of discussion and often got confused with various other psychological and neuronal disorders (Altschuler 2001). The story of the disorder is complicated than the disorder itself. In this book, we have covered diagnosis, treatment, and effects of SZD in individual life, but the importance to differentiate it from the other mental disorders is very important. It is a challenge for the researchers and the people in the medical field. There have been several theories about it. In this chapter, we have selected five major mental disorders to draw a differentiating line between them. The focused mental disorders are:

1. Schizophrenia (SZD).
2. Alzheimer's disease.
3. Parkinson disease.
4. Chronic depression.
5. Bi-polar disorder.

The reason to select the above five mental distresses is, they all have a similar like spectrum and often get confused until a very late stage. Especially symptoms like brain fogging, acute stress or anxiety, memory-related issues, and social and emotional withdrawal are there in each spectrum of the selected disorders (Arya et al. 2018; Jankovic 2008; Bansal and Chatterjee 2021; Crespi 2016). In this chapter, we have tried to explore and intensify the smallest difference among the selected mental disorders.

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5.2 Schizophrenia

SZD is one of the most chronic mental disorders which have affected more than 1% of the entire global population (Chatterjee et al. 2020). Symptoms of SZD can be broadly divided into two types: positive and negative symptoms. Positive symptoms mean the symptoms which can be observed, whereas negative symptoms mean symptoms which cannot be observed physically. Positive symptoms include hallucination, delusion, and disorganized behaviour. Negative symptoms include affective flattering, attention impairment, alogia, etc. (Chatterjee and Mittal 2020). Despite so many prominent symptoms the challenge is, all these symptoms progress and are visible after a specific period of time. Usually, these symptoms strike in the age group of 40–45 years, very often between 20 and 35 years and rarely between the age group of 10 and 19 years (Chatterjee et al. 2020). Thus, often, it was found that the delay in starting the treatment had worsen the symptoms are health of the patient. However, a clinical tool designed by a German psychiatrist Kurt Schneider (Marneros et al. 1987) has shown positive results in predicting the chances of SZD. This tool is known as "first-rank symptoms" (FRS) (Marneros et al. 1987) and has helped the medical people in starting personalized treatment before the disorder progress. Table 5.1 summarizes the Schneider's FRS classical model. Different studies (Marneros et al. 1987; Malinowski et al. 2019; Mellor 1970) have reported that few aspects of the FRS model are useful in predicting the onset of psychiatric disorder which can eventually help in early personalized treatment.

According to the World Health Organization (WHO)[1] and American Psychiatric Association's Diagnostic and Statistical Manuals (DSM),[2] there are three basic steps to diagnosis the onset of SZD in an individual.

1. Showing two or more symptoms like delusion, hallucination, disorganized speech, catatonic behaviour, emotional and social withdrawal.
2. Showing the symptoms for more than a month.
3. No response to the medications.

If all the above three conditions are fulfilled, then an individual can be put in the SZD category. Once a patient is identified as a SZD patient, s/he is advised to go through different clinical tests. These tests help the medical experts in understanding the stage and type of SZD.

Starting from personal to professional, from social to daily life, SZD disturbs every aspect of an individual's life. To avoid mixing this disorder with some other, we need to understand the other disorders. Let us discuss the other four mental disorders in depth and then reconnect them to SZD later in this chapter.

[1] World Health Organization. (n.d.). *Schizophrenia*. World Health Organization. Retrieved May 25, 2022, from https://www.who.int/news-room/fact-sheets/detail/schizophrenia

[2] *DSM*. Psychiatry.org - DSM. (n.d.). Retrieved May 25, 2022, from https://psychiatry.org/psychiatrists/practice/dsm

Table 5.1 Schneider's FRS tool deduction method (adapted from Malinowski et al. 2019; Mellor 1970)

Terms	Other terminology	What should be observed
Auditory hallucinations		
• Audible thoughts	Gedankenlautwerden	Patient/s believes their thoughts are spoken aloud by some other voice
• Voices arguing		Patient/s hears two or more people talking or arguing
• Voices commenting on one's action		Patient/s believes their actions are controlled or guided by someone else
Influence playing on the body	Somatic passivity	Patient/s experience sensation likes touch, thought and emotions as if induced by someone else
Thought withdrawal		Patient/s believes their thoughts are being removed by someone in their head
Thoughts ascribed to others	Thought insertion	Patient/s believes there are thoughts inserted by external force in their head
Broadcasting of thoughts	Diffusion of thoughts	Patient/s believes their thoughts are diffused in the world by some external force.
"Made" feelings		Patient/s experience feelings which they deny to be theirs
"Made" impulses	Drives	Patient/s believes that due to a sudden impulse by an external force they perform action which they do not want to do
"Made" volitional acts		Patient/s experience their actions are controlled by someone else. They either initiate or end the action
Delusional perception		Patient/s takes the normal perception in an illogical and meaningless way

Source: Malinowski et al. (2019) and Mellor (1970)

5.3 Alzheimer's Disease

During early 1900, a group of curious psychiatrists identified an abnormal protein accumulating in the human brain. This protein was identified as amyloid-β and Tau. Due to this protein, neurofibrillary tangles and plagues were observed in the neurons and lead to shrinkage of the brain (Khachaturian 1985). When Alois Alzheimer in 1907 presented his study on this problem during a meeting of the Society of Southwest German Psychiatrists, this disease was named after his name as Alzheimer's disease (AD). Nowadays AD is one of the most common mental disorders but with no cure (Goedert and Spillantini 2006).

After decades of intense research, researchers finally found the effects of AD on the human body. Shrinking volume brain brought number of hypothesis but only a few turned out to be true. Table 5.2 summaries all the symptoms experienced by an AD patient in different stages of AD.

Table 5.2 Stages and symptoms experienced by AD patients (Katzman 1986; Goedert and Spillantini 2006)

Stage	Symptoms
Early stage or mild stage	Experience memory lapses and cognitive disabilities, difficulties in performing daily or routine tasks like answering questions, handling finance
Middle stage	Experience trouble in speaking and accomodating thoughts. Areas controlling language, logical reasoning, senses and thoughts are affected. (This can be traced in different brain scans)
Last stage	Complete loss of memory, communication and cognitive abilities. Bedridden and dependable on caregivers

AD is a slow progressive disorder. The longest stage of AD is the middle stage. Even before the early stage, there are some prominent symptoms which can help in the identification of the disorder at a very early stage. The following symptoms could be observed and discussed with a doctor (Katzman 1986):

(a) Loss of memory.
(b) Difficulty in dealing with numbers.
(c) Taking more time to complete regular tasks.
(d) Trouble remembering and writing events.
(e) Changes in communication skills (not efficient as before).
(f) Frequent mood swings.
(g) Social and emotional withdrawal.
(h) Difficulty in making decisions.

According to the above list, symptoms like changes in communication skills, frequent mood swings, and social and emotional withdrawal could be confused with the symptoms of SZD. SZD is said to be a chronic psychiatric disorder caused due to various reasons, whereas AD is a complete neurodegenerative disorder caused due to plague formation (Kochunov et al. 2021). However, both have overlapping symptoms like cognitive impairment, changes in the white and grey matter, and memory-related issues (Kochunov et al. 2021). Thus, to avoid such confusion, there are different diagnostic methods developed for AD and SZD. When diagnosing AD, the clinical experts start from family history to current medications and the Doctors will question everything. If any family history of AD is found, then they directly recommend for scans; else they precede with cognitive, memory-based and behavioural tests (Khachaturian 1985). Though these tests are sufficient to identify the disorder, but if in any confusion then, the patient is taken for different scans. These scans help the medical people identify the protein deposition and start with the treatment of AD.

Currently, there is no cure for AD but there are five clinically approved medications given to AD patients to slow down the shrinking process (Mayeux and Sano 1999). AD should not be confused with dementia. Dementia is caused by any changes in the amyloid-β and Tau protein. AD is a type of dementia due to continuous shrinkage in the brain so that the patient suffers complete loss of memory and cognitive abilities (Katzman 1986).

5.4 Parkinson Disease (PD)

Surprisingly, PD was identified way before AD and SZD. Back in 1817, James Parkinson wrote a monograph titled, "Essay on Shaking Palsy" where he described all the clinical features of a neuronal disorder. Which later was named after his name as Parkinson's disease (PD) (Dauer and Przedborski 2003). PD is an age-related disorder in which the substantia nigra pars compacta (SNPC) experience complete loss of neurons (Dauer and Przedborski 2003). Later it was discovered that SNPC is the critical brain region associated with the production of dopamine (DA) (Cheramy et al. 1981). Various relevant studies identified different roles of DA like controlling cognitive and body moment, regulating mood, and helping in release of emotions. Therefore, changes in the level of DA can cause various dysfunctioning.

Considering the clinical symptoms of PD, it was found that due to deficiency of DA in the brain there are various symptoms experienced by the patients. Researchers divided all the symptoms into two types: motor and non-motor symptoms (Davie 2008). Table 5.3 summarizes all the symptoms experienced by the PD patients.

According to different relevant researchers (Warner and Schapira 2003), following are the major causes of PD:

(a) Genes: With very limited cases of heredity, the scientists are still in progress to identify the role of gene in causing PD.
(b) Environmental factors: Researchers believe that certain toxic chemicals can cause PD by killing the DA neurons in the SNPC.
(c) Lewy body: A clumps substance found in the PD patients' brain is one of the most fascinating things for the researchers. They strongly believe that the presence of alpha-synuclein (a-synuclein) in these Lewy bodies hold some direct connection with PD.
(d) Age and sex: There are hardly any young or teenage PD patients. PD is believed to be an old age neuronal disorder. Usually, affect men the most.

When focused upon the treatment of PD, it was observed that levodopa (Church 2021) was able to control the symptoms of PD but later majority of patients developed an involuntary moment termed "dyskinesia." The reason behind the

Table 5.3 All major symptoms experienced by PD patients (adapted from Church 2021)

Motor symptoms	Non-motor symptoms
Resting tremor	Idiopathic hyposmia
Postural instability	Neuropsychiatric disorders like depression/anxiety, psychosis/hallucination, impulse control disorders and apathy
Bradykinesia/ hypokinesia	Cognitive impairments like confusion, dementia, impairments in memory, executive functions and visuospatial skills
Muscular rigidity	Autonomic disorders like HRV alterative, urinary dysfunction, orthostatic hypotension, gastrointestinal dysfunction and sexual dysfunction
	Sleep disturbance which includes insomnia, sleep disorders, excessive daytime sleepiness

same is still a research interest. However, a medication procedure to control or halt the death of DA neurons in the SNPC is still not known.

Changes in the DA level are directly linked to PD and SZD. Thus, both can show some common symptoms like depression, anxiety and loss of pleasure but there are some major differences between PD and SZD. These differences are due to changes of DA level in different parts of the brain. When a person suffers from PD the changes are observed in the SNPC area which is the mesostriatal pathway of DA (Birtwistle and Baldwin 1998). Whereas during SZD the DA pathways which are affected are mesolimbic and mesocortical pathways which involve brain regions like frontal and temporal lobes (Birtwistle and Baldwin 1998). Therefore when the affected pathways are different in both the disorder, the number of similarities between PD and SZD decreases and difference increase. However, the confusion between the two mental disorders could be observed at an early state of diagnosis.

5.5 Chronic Depression (CD)

To understand the connotation of CD, we need to understand the meaning of depression. The meaning of depression has changed over time but we stick to the meaning given by the WHO. According to the WHO,[3] depression is a common mental disorder in which an individual constantly experiences unpleasant emotions (like sadness, anxiety, and low motivation). Along with unpleasant emotions, the individual face issues in enjoying or feeling pleasure in the things s/he use to enjoy before. Over 5% of the global population experience depression due various reasons (Paykel 2008). An individual is diagnosed with depression only if the above symptoms persist for more than two continuous months. There are different forms of depression disorders (like: bipolar, major, atypical, melancholic, minor, mixed, and seasonal effective) (Benazzi 2006). In case the symptoms worsen and persist for more than 2 years, then the same is diagnosed as CD (Seemüller et al. 2022). CD can further be sub-divided into four types (Jobst et al. 2016):

- Dysthymic disorder.
- Chronic major depression disorder.
- Double depression.
- Recurrent major depression disorder with incomplete recovery between episodes.

According to the recent available literature, the above-mentioned types of CD have more similarities than differences, and can be seen under the “CD Spectrum Disorder” (Jobst et al. 2016).

[3] World Health Organization. (n.d.). Depression. World Health Organization. Retrieved May 17, 2022, from https://www.who.int/health-topics/depression#tab=tab_1

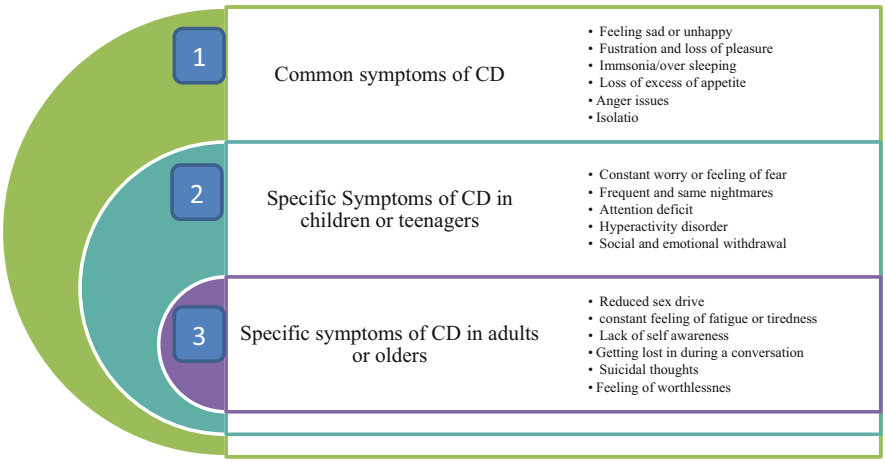

Fig. 5.1 Representing CD symptoms according to different age group. Represents all the (1) common symptoms of CD, (2) symptoms of CD experience by children or teenagers, (3) symptoms of CD experienced by adults or older (Kumar et al. 2012)

When we talk about causes of CD, there is a long list. Causes of CD can vary from individual to individual. Below is the list of all the major causes of CD stated by different researchers and psychiatric organizations (Kumar et al. 2012):

• Childhood adversity	• Alcohol or drug abuse
• Continuous stressful situations	• Serious medical complications
• Isolation	• Steroids or anti-psychotic medications
• Anxiety issues	• Emotional trauma

Even the symptoms of CD can vary from patient to patient. Figure 5.1 is a representation of all the major symptoms patients can experience according to their age. According to relevant literatures, a person who experiences more than any two symptoms should consult a medical adviser before his/her symptoms worsen any further (Kumar et al. 2012).

The diagnosis of CD can be done at a primary stage, if the symptoms are recorded effectively. CD diagnosis starts with self-realization. When a person can observe his/her changing behaviour and seek medical help soon, they can avoid worsening of their symptoms. The medical experts look for more than two symptoms in the patients and note the time duration. The experts also ask different questions to understand the potential cause behind depression or CD. The experts on the basis of severity of the symptoms and cause behind the same advise treatment. Treatment of CD could include medicines, exercise, yoga, meditation, counselling sessions, and even rehabilitation groups. If the patients do not respond to the treatment, then experts advise for various scans just to eliminate any changes of order disorders.

Often a very common question arises "*Can depression or CD turn into a serious mental disorder?*" and the answer for it is "Yes." As per the available literature, there

are three approaches which can define how depression turns into mental disorders (Maj 2011):

1. Contextual approach.
2. Qualitative approach.
3. Pragmatic approach.

When spectrums of different mental disorders were studied, then depression and CD were identified at an initial stage in each spectrum. It has been a challenge for the researcher to understand the prevalence of depression in SZD. Researchers have linked mood stability, depression, and SZD together. SZD is not the affect, symptoms, or syndrome of depression. Depression is a characteristic trade of SZD but not true for all the patients. Since, dopamine is considered as the pleasure or reward giving neurotransmitters, few researchers have also linked it with depression (Mauri et al. 1995). However, this concept needs more in-depth analysis. A major difference between CD and SZD is even after prolong CD, the patients do not experience any functional or structural changes in the brain as they do in SZD.

5.6 Bi-Polar Disorder

When talking about depression and its various types, it is important to highlight the manic-depressive disorder also known as bipolar disorder (BD). The major characteristics to identify BD are constant fluctuations in state of mood and energy. With one of the highest mortality rates, BD has affected more than millions of people around the globe (Grande et al. 2016). Still the clinical diagnosis of BD at an initial phase is tough because it looks more likes unipolar depression. Thus, to avoid any mistake in the diagnosis, a continuous examination and assessment is required. There are different psychological and pharmacological strategies available for treating BD (Grande et al. 2016).

According to relevant literatures, reasons like living conditions, marital status, employment, mood, medications, physical exercise, and family history of BD can trigger the very first episode of BD (Kupfer et al. 2022). When the triggering point of BD could be any emotional or mental distress thus looking for its characteristic traits is very important. According to DSM 5th[4] edition, Table 5.4 summarizes all the similar kind of disorders and their respective diagnostic trait.

When looking for relationship between SZD and BD, it turned out that they have a lot of symptoms similar between them. The differentiating factor among them could be the positive symptoms like hallucination and disorganized speech during SZD. The grey and white reduction during SZD is also a major differentiating factor among the two (Chatterjee 2018). Figure 5.2 demonstrates the overlapping symptoms of SZD and BD.

[4] "DSM." *Psychiatry.org - DSM*, https://psychiatry.org/psychiatrists/practice/dsm

Table 5.4 BD and similar disorders with their diagnostic characteristic trait (Grande et al. 2016)

Disorder	Diagnostic characteristic trait
BD I disorder	Prevalence of one bi-polar episode
BD II disorder	Prevalence of one hypomanic and one major depression episode
Cyclothymic disorder	Prevalence of hypomanic and major depression episodes for more than 2 years
Unspecified and related BD	Symptoms do not fit in any criteria. They could be induced due to some drug or some other medical conditions
Other specified and related BD	Due to insufficient duration or severity, they do not match any criteria. Therefore, they are referred as short duration of short-lived BD

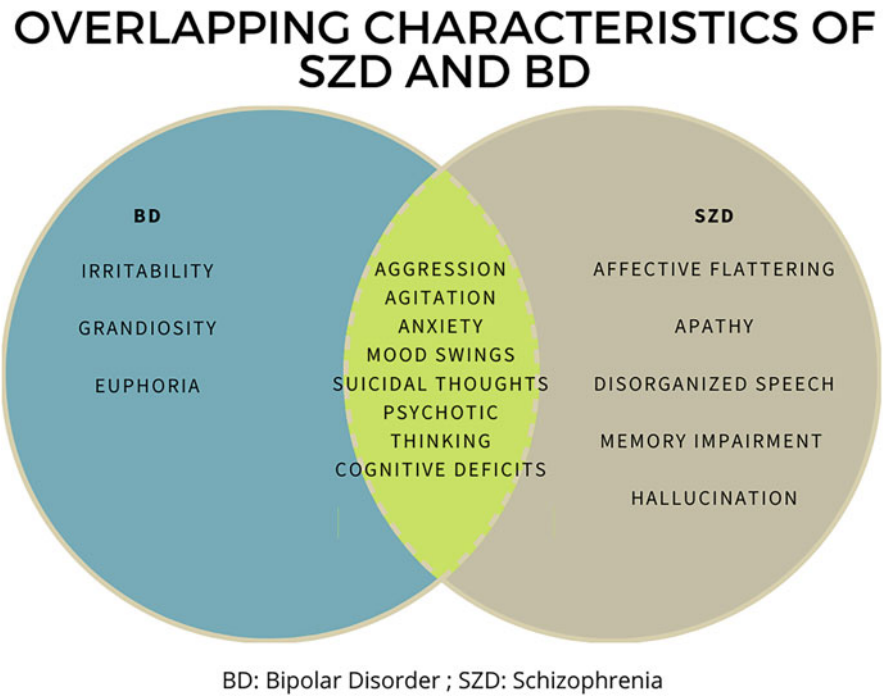

Fig. 5.2 Demonstrating the overlapping symptoms of SZD and BD. (Adapted from Keck et al. (2001) and Crespi (2016))

5.7 Conclusion

When an individual deals with any mental, neurological, neurodegenerative, or psychotic disorders, then they lose a part of their identity. The patient loses control on things and activities which seemed normal to them. Losing contact with the reality and experiencing unfamiliar emotions or symptoms could be hard for anyone.

During SZD, the patient is not able to draw a line between hallucination and reality. They fear to share their unrealistic experience with someone seems hard to

them. Psychologically, they are challenged to understand the difference what is real and imaginary. Therefore, constant counselling sessions and talking therapies are needed. Similarly, during AD, when the patient start losing his/her memory and start facing difficulty in daily activities, they withdraw themselves from their surroundings. During AD, if the symptoms are recognized at a very initial stage, then the process of the brain shrinking could be delayed but never stopped. The frustration of inefficiency to recognize people and self-realization often leads to suicidal thoughts. Even today we do not have an efficient treatment for AD.

After decades of research, PD and SZD are studied together since both are associated with the deficiency of DA in the human brain. PD is diagnosed when there is complete loss of DA in the SNPC region. From SN, the nigrostriatal pathway of DA is extended towards the corpus striatum which is one of the brain regions involved during SZD. However, the mesolimbic and mesocortical pathways of DA are much more involved in triggering the symptoms of SZD. Thus, according to the researchers, it is important to manage psychosis during PD effectively. The level of DA could also be influenced by the gut-brain relationship. Different vitamins are capable to trigger the DA receptors (Bansal and Chatterjee 2022).

When spectrums of various mental disorders were observed, the presence of few episodes of depression was acknowledged. CD and BD were among them. Both CD and BD are different in their characteristics, but episodes of them can be linked to other serious mental disorders. BD holds higher mortality rate as compared to CD.

Finally, to sum-up, a major observation could be drawn that other than genes there are two effective ways to trace SZD: one is through continuous monitoring of the symptoms and the other is to trace any functional and structural changes in the brain.

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Chapter 6
Neurobiological Aspects of Schizophrenia and Relationship Between Neurological Disorders: Depression, Anxiety, and Epilepsy

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Schizophrenia is a mental disorder, which is associated with neurological disorders such as depression, anxiety disorder, and epilepsy. Although these disorders like schizophrenia, depression, and anxiety disorder appear emotional symptoms negatively for patients, these problems affect humans' nervous system and brain functions directly and then induce epilepsy finally. Especially, the patients have brain abnormalities and cognitive problems. This study identifies the issue neurobiologically more than pathologically or medically as we know. Firstly, schizophrenia causes the nervous system and brain functions such as the cerebrum, cerebellum, white matter, and gray matter. These phenomena are associated with neurotransmitters occurrence even, like dopamine, glutamate, etc. Secondly, depression and anxiety disorder have comparable symptoms physically and mentally. Both affect the digestive system, fatigue, and psychological difficulties. Therefore, people have these disorders in trouble with social activity in particular. Finally, those mental disorders reach epilepsy. The main point of epilepsy is epileptic seizure. The reason for the seizure is mental illness and also the mental disorders produce the epileptic seizure correspondingly. Until now, not able to treat completely the epilepsy yet, but control emotional problems properly is one of the best ways to manage the symptoms of epilepsy.

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6.1 Introduction

Schizophrenia is a mental disorder highly related to other mental disorders such as depression and anxiety disorder and even connected to a neurological disorder, epilepsy. Schizophrenia is a psychotic disorder with major symptoms including hallucinations, delusions, etc. The anxiety disorder is also a mental disorder that is involved in uncontrollable feelings, fears, and depression that reveal mainly loss of interest or pleasure in normal life. However, these disorders belong to pathology (Iritani 2013) and the psychotic disorders and mental disorders are caused by brain mechanisms (Till et al. 2019), so that these problems can explain neurobiologically.

Once, this review shows the brain structure and functions for analyzing the mental disorders with epilepsy easily. Next, describe schizophrenia such as symptoms of disorders, complications, and risk factors. The most important is that change the brain structural integrity with schizophrenia to figure out the neurobiological mechanisms of schizophrenia (Chatterjee et al. 2020a, b). Moreover, neurotransmitters of the brain when schizophrenia has occurred. Lastly, describing depressive disorder and anxiety disorder. In particular, it is acknowledged that sub-types of these disorders and also the certain neurotransmitters lead to depressive disorders and anxiety disorders. Finally, outline the mental disorders above. Eventually, considering how the mental disorders are connected to epilepsy which is involved in schizophrenia (Maguire et al. 2018).

6.2 Neurobiology of a Brain and How Brain Works

6.2.1 Brain

The brain is a complex organ (Pena-Casanova 2018) that is related to humans' physical and emotional area as well. Therefore, in connection with the brain, there are not only physical disorders but also many types of mental disorders. Several mental disorders and psychological disorders are caused by features of separated brain structures. The brain is divided into accurate regions with certain functions. Therefore, researching the brain differently is necessary to understand the different conditions such as medical methods, chemical methods, biological methods, etc. In the case of the neurobiological methods are focused on the nervous system combined with biology. Also, the major regions and abilities of the brain are fields of neurobiology.

6.2.2 What Is Neurobiology?

It is difficult to simplify the definition of the term "neurobiology" itself. However, the concept of neurobiology may less vague if the research is focused on the brain disorders. Therefore, neurobiology is a branch of biology that deals with the nervous

system functions and structures to study the mechanisms which is associated with the neurological system. The term "neurobiology" is different between "neuroscience" and "neurology". The biological aspect is the key distinction of neurobiology.

6.2.3 Nervous System

The nervous system is divided into two major sections: the peripheral nervous system (PNS) and the central nervous system (CNS). The CNS consists of the brain and spinal cord. The PNS consists of the nerve tracts that connect the rest of the body to the central nervous system. The central nervous system is composed of the brain and spinal cord. The brain is a complex organ that controls every process that regulates human body. It means that the brain manages sensor systems, memories, consciousness, emotions, temperature, hunger, breathing, etc. The brain contains two major regions that are gray matter and white matter.

6.2.3.1 Gray Matter and White Matter

Gray matter and white matter are two different regions of the CNS. The gray matter is the stuff on the outer surface of the brain tissue which is composed of neuron somas (the round central cell bodies), while the white matter is located on the inner side. The gray matter lacks myelin which is responsible for the processing and regulating of information, whereas the white matter is myelinated axon that long-distance wires transmit information to other parts of the nervous system. The white matter is made up of three types of fibers, commissural fibers, association fibers, and projection fibers.

6.2.4 Brain and Functions

The brain is clearly separated into different parts with diverse functions. It is difficult to describe the brain structures in details. Typically, there are major parts of the brain to understand cerebrum, cerebellum, and the brain stem. Each structure plays a key role in ways.

6.2.4.1 Cerebrum

The cerebrum is divided into the right hemisphere and the left hemisphere. The right cerebral hemisphere is responsible for the interpretation of nonlinguistic stimuli such as facial expressions, body languages, gestures, prosody, melody, rhythm, and environmental sounds: understanding macrostructure; visuo-spatial processing;

and attention (sustained and selective). On the contrary, the left cerebral hemisphere refers to expressive and receptive language abilities. Broce's area and Wernicke's area are parts of the left cerebral hemisphere that is responsible for the expressive language and receptive language each. In addition, the cerebrum is divided into four lobes: frontal lobe, parietal lobe, temporal lobe, and occipital lobe.

- *Frontal lobe*: located in the front of the brain.
  - Personality, behavior, emotions.
  - Judgment, planning, problem solving.
  - Speech: speaking and writing (Broca's area).
  - Body movement (motor strip).
  - Intelligence, concentration, self-awareness
- *Parietal lobe*: located behind the frontal lobes.
  - Interprets language, words.
  - Sense of touch, pain, temperature (sensory strip).
  - Interprets vision, hearing, sensory, and memory.
  - Spatial and visual perception
- *Occipital lobe*: located back of the brain.
  - Interprets vision (color, light, and movement)
- *Temporal lobe*: located on the side of the brain.
  - Understanding language (Wernick's area).
  - Memory.
  - Hearing.
  - Sequencing and organization.

6.2.4.2 Brain Stem

The Brain stem is located near the bottom of the brain. A large portion of the brain stem is involved in autonomic control of the body such as functions of the heart, blood vessels, etc. The brain stem includes the medulla, pons, and midbrain.

First of all, the bottom part of the brain stem and the medulla are related to transmit signals between the spinal cord and the higher parts of the brain. Regulating the function of the medulla involves the control of blood pressure, breathing, balance, taste, hearing, and the control of muscles of the face and neck.

Secondly, the pons in the brainstem is situated between the midbrain and the medulla oblongata. Pontine nuclei (nuclei of the pons) provide principle input to the cerebellum. The pons, the middle portion of the brainstem coordinates regulation of respiration, control of involuntary actions, sensory roles in hearing, equilibrium, taste, and facial sensations such as touch and pain, as well as motor roles in eye movement, facial expression, chewing, swallowing, and the secretion of saliva, and tears.

Finally, the midbrain is the most region of the brain stem, also called mesencephalon. Tectum and tegmentum make up the midbrain, also known as the mesencephalon, a part of the growing vertebrate brain. The midbrain is involved in motor movement, particularly eye movements, as well as auditory and visual processing.

6.2.4.3 Cerebellum

The cerebellum is located behind the pons, between the cerebrum and the brain stem. The cerebellum has a relatively small portion of the brain, almost 10% of the total weight. However, over half of the neurons of the brain exist in the cerebellum. Functionally, the cerebellum controls posture and coordinates the movements of body parts such as eyes and head as well as the limbs are functions.

6.3 What Is Schizophrenia and How It Changes the Structural Integrity of the Brain?

6.3.1 Schizophrenia

Schizophrenia is a severe brain disorder in which people live in delusions and hallucinations (Chatterjee et al. 2019). More than these symptoms are caused by chemical imbalances, brain abnormalities, genetics, environmental factors, etc. There is no cure for this illness, but it can be managed with medicine and supportive therapy (Ross et al. 2006).

6.3.1.1 Symptoms

There are three major categories of schizophrenia symptoms that are positive symptoms, negative symptoms, and disorganized symptoms (Chatterjee et al. 2019).

1. Positive symptoms.
   (a) Hallucinations (auditory, visual, haptic, or olfactory).
   (b) Delusions.
   (c) The repeated occurrence of disorganized behavior.
2. Negative symptoms.
   (a) Affective flattening.
   (b) Anhedonia Asociality.
   (c) Avolition-apathy (e.g., impersistence, anergia at work).
   (d) Attentional impairment.
   (e) Alogia (e.g., poverty of speech, poor content of speech).

3. Disorganized symptoms.

   (a) Disordered thinking and speech.
   (b) Trouble with logical thinking.
   (c) Bizarre behavior or abnormal movements.

6.3.1.2 Reasons for Schizophrenia

The causes of schizophrenia are not accurate. However, a combination of genetics, brain chemistry, and environment contributes to the development of the disorder. Therefore, the types of factors below may affect schizophrenia.

- Genetics.
- Development of the brain.
- Neurotransmitters.
- Birth complications.
- Social and personal triggers.
- Drug intake.

6.3.2 Changes the Structure Integrity of the Brain

Schizophrenia induces structural changes in the human brain widespread. According to several studying, the brain structural phenomenon in schizophrenia is related to ventricular enlargement (Shenton et al. 2001; Antonova et al. 2004), cortical thickness (Penadés et al. 2019), brain volume loss (Shenton et al. 2001), etc. Also, each part of the brain regions changes separately. Neurobiologically, the gray matter is a major component of the brain. The brain region exhibits the gray matter atrophy in schizophrenia (Chatterjee et al. 2020a, b).

Volumetric gray matter loss in several brain regions such as the insula and superior temporal gyrus regions have been identified (Chatterjee et al. 2020a, b). Significant reductions in the regional grey matter were also revealed in the medial temporal lobe (Chatterjee et al. 2020a, b; Shenton et al. 2001; Gilbert & Keshavan 2001). At the hemisphere level, the left and the right hemispheres reduce gray matter concentration in schizophrenia patients. However, there are no changes in the gray matter volume in the brain stem or cerebellum region (Karlsgodt et al. 2010; Chatterjee et al. 2020a, b).

6.4 How Schizophrenia Brain Acts as Disorder Neurobiologically

6.4.1 Neurobiology of Schizophrenia Brain

Neurobiology defines the biology of the nervous system, so that neurobiology of the schizophrenia brain means the nervous mechanism of the brain with schizophrenia symptoms (Ross et al. 2006). The mechanism of schizophrenia is based on the development of the disorder (Bateman & Nacke 2010). Typically, the neurotransmitters attempt to demonstrate the link between the causes of schizophrenia and brain function and the development of schizophrenia. Dopamine and Glutamate are neurotransmitters to explain the brain in schizophrenia. However, dysfunction of the interneurons, immune systems, and oxidative stress is also considered in the schizophrenia brain.

Once, dopamine is called the neurotransmitter or brain messenger chemistry in schizophrenia. Due to excess of the dopamine neurobiologically, positive symptoms of schizophrenia such as hallucinations and delusions have occurred (Role of neurotransmitter, Indra's). In details, the symptoms are caused by increased subcortical release of dopamine which is D2 receptor activation (Shenton et al. 2001) due to an altered cortical pathway through the nucleus accumbens.

Besides the dopamine neurotransmitter, glutamate, and function reduction of N-methyl-d-asparate (NMDA) glutamate receptor are involved in neural process of the brain with schizophrenia. In particular, lower levels of glutamate receptors are found in the postmortem brains of people diagnosed with schizophrenia. Reduced messenger RNA (mRNA) and protein expression of several N-methyl-D-aspartate glutamate receptor (NMDA glutamate receptor) are also reported in postmortem brains of individuals with schizophrenia. Glutamate deficiency in the brain is supposed to cause psychotic symptoms and psychotic disorders as well (neurotransmitter and brain parts involved in schizophrenia).

6.5 What Depression and Anxiety Affect Neurobiologically

6.5.1 Depression and Anxiety

Depression and anxiety disorders are among the most common illnesses in the community and in primary care (Adwas et al. 2019). Patients with the depression often have features of the anxiety disorders, and those with anxiety disorders commonly also have depression. Both disorders may occur together, meeting both criteria. It can be difficult to discriminate between them, but it is important to identify and treat both illnesses, as they are associated with significant morbidity and mortality. General practitioners are well placed to identify and take a primary role in the treatment of these illnesses to facilitate better mental health outcomes.

6.5.1.1 Depression

Depression is a mental disorder characterized by pervasive low mood, low self-esteem, and loss of interest or pleasure in normal life (Palazidou 2012). And, symptoms of depression include poor concentration and memory, withdrawal from social situations and activities, reduced sex drive, irritability, and thoughts of death or suicide. Insomnia is common: in the typical pattern, a person wakes very early and cannot get back to sleep. Hypersomnia or oversleeping can also happen. In severe cases, depressed people have psychotic symptoms. These symptoms include delusions or hallucinations. In addition, physically, depressed people have fatigue, headache, or digestive problems. Furthermore, appetite decrease results in weight gain or loss. Depression is caused by a combination of genetic environmental factors and psychological factors. Also, relationships between neurotransmitters affect specific symptoms of depression as well.

Three main monoamine neurotransmitters in the brain, dopamine, norepinephrine, and serotonin are reasons for specific symptoms of the depressive disorder (Chatterjee & Mittal 2020). If dopamine, norepinephrine, and serotonin in the brain reduce respectively, depressive people would have certain problems with depression.

Symptoms

- Low levels of Dopamine.
  - Hopelessness and dread.
  - Low self-esteem and self-worth.
  - Trouble starting and finishing projects.
  - Losing our temper after a minor setback.
  - Difficulty managing stress.
  - Anger, irritability, and aggressiveness.
  - Apathy toward family and friends.
  - A desire to be alone or isolated.
- Low levels of Serotonin.
  - Dissatisfaction or feeling unhappy, frustrated, and angry.
  - Trouble staying positive or experiencing a lack of joy.
  - Difficulty falling asleep, staying asleep, and feeling well-rested.
  - Consistent low mood.
  - Losing pleasure in things we once enjoyed.
- Low levels of Norepinephrine.
  - Anxiety.
  - Migraine headaches.
  - Loss of alertness.
  - Lack of arousal and interest in doing things.

- Foggy brain and trouble concentrating.
- Feeling unmotivated.
- Fatigue.

6.5.1.2 Anxiety Disorder

Anxiety disorder is a mental disorder. The disorders are characterized by significant and uncontrollable feelings of anxiety and fear such that a person's and personal function are impaired. Anxiety causes physical and cognitive symptoms such as restlessness, irritability, easy fatigue, difficulty concentrating, increased heart rate, chest pain, abdominal pain, and various other symptoms individually (Adwas et al. 2019).

There are several types of anxiety disorders that include generalized anxiety disorder, specific phobia, social anxiety disorder, separation anxiety disorder, agoraphobia, and panic disorder. Generalized anxiety disorder includes persistent and excessive anxiety and people with the disorder worry about normal happens, even routine issues. The issues are difficult to control and can be affected physically. Moreover, Specific phobia is a major anxiety when people are exposed to certain objects or situations and desire to avoid these. Social anxiety disorder is high-level anxiety which is fear and avoidance of social situations due to feel embarrassment, self-consciousness, and worry about being judged or viewed negatively by others. Separation anxiety disorder is for childhood disorder with excessive anxiety which is involved in child's developmental level and separated from parents or others who have parental roles. Agoraphobia is an anxiety disorder in which people fear and avoid places or situations that might cause panic and make feel trapped and helpless or embarrassed. The last, panic disorder is associated with repeated episodes of sudden feelings of intense anxiety and fear or terror that reach a peak within minutes (panic attacks). Panic attacks lead to people worry about happening again or avoiding situations in which it is occurred. Abnormal functioning of neurochemicals, neurotransmitters lead to anxiety. Symptoms of anxiety and anxiety disorders affect physical symptoms and some negative feelings as well.

- Physical symptoms.
  - Increase heart rate.
  - Breathing rapidly (hyperventilation).
  - Sweating.
  - Trembling.
  - Have cold related to fatigue.
  - Dizziness.
  - Muscle pain.
  - Indigestion.
  - Headache.
- Negative feeling symptoms.

- Having difficulty controlling worry.
- Feelings of danger.
- Nervousness.
- Restlessness.
- In the panic.

6.6 How Epilepsy and Schizophrenia Connected Depression and Anxiety Disorder

6.6.1 Epilepsy

Epilepsy is neurological disorder, not an illness characterized by recurrent epileptic seizures and other different reasons (Maguire et al. 2018). Typically, epileptic seizure is the reason for electrical activity in the brain. Schizophrenia is a risk factor for epilepsy and seizure that include cognitive problem (Hyde and Weinberger 1997; Maguire et al. 2018). Also, the depressive disorder and the anxiety disorder are types of cognitive problems, so that depression in people living with epilepsy is very common and an important issue. Moreover, anxiety disorder is related to the depressive disorder as well (Jackson and Turkington 2005).

6.6.2 Anxiety Disorder and Depression and Epilepsy

Anxiety is significant in the life of a people with epilepsy. In any medical illness, many people become anxious after the diagnosis of their condition (Hingray et al. 2019). However, anxiety is also related to epilepsy in more specific ways. Not only reaction to the diagnosis of epilepsy but also symptoms of epilepsy or side effects of seizure medicine are the reasons for anxiety. In particular, people have their first seizure when they develop anxiety after epilepsy is diagnosed. In fact, the most common cause of anxiety is the fear of having a seizure. Therefore, causes of epilepsy are believed to play a role in the development of anxiety (Kwon and Park 2014).

Furthermore, depression acts as an aura for some people with epilepsy. An aura is a warning sign that a seizure is coming. It means that feeling depressed strongly after frequent epileptic seizure. On the other way, the seizure affects more severe depression for people with epilepsy (Hyde and Weinberger 1997).

Totally, the disorders of anxiety and depression are a big risk of epilepsy and schizophrenia. Schizophrenia is also associated with epilepsy. Although there is proper support for symptoms of these enhancing problems, there is no accurate way to treat these issues medically (Cascella et al. 2009).

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Chapter 7
Clinical Treatment Available for Schizophrenia

Papiya Ghosh

7.1 Introduction

Schizophrenia is a chronic mental disorder, with multiple disabilities which lead to poor quality of life (World Health Organization 2019). The prevalence rate of schizophrenia worldwide is 1% irrespective of culture, race and ethnicity (Bansal and Chatterjee 2021). Schizophrenia also affects both male and female gender equally. The patients mainly present with hearing voices that others cannot hear, suspiciousness and false belief that people want to harm them or follow them. Following this, the patient usually become aggressive and agitated which can cause harm to others or self. All the above symptoms lead to withdrawal from society, fear, loss of job or maybe discontinuing studies. All these result in depression and poor social life (World Health Organization 2019).

Schizophrenia patients are found all over the world. Medications are widely available to treat the illness when it is properly taken as per the psychiatrist's prescription. But medication non-adherence led to multiple disabilities. It can be due to various causes. Patients' knowledge regarding illness, stigma, attitude towards the psychotropic medication, number of pills, cost of the medications, unavailability of prescribed medication and side effects of medication factors can lead to medication non-adherence (Sadock et al. 2015; Chatterjee 2018).

Schizophrenia has already been detailed in a previous chapter. Now our focus will be on the treatment of schizophrenia. When a patient is treated with appropriate medications, it improves symptoms, makes the patient independent and improves the quality of life. But sometimes even with medications, the treatment remains ineffective and patients develop resistance to the current treatment. Resistance to medications further leads to loss of jobs, studies, stigma and isolation from the

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family and society which may be troubling for the schizophrenia patients (Ahuja 2017).

Schizophrenia not only has an impact on the patient life but also on caregivers. It can lead to a huge caregiver burden. So, the treatment plan includes not only the patient but also the family members as well (Grover et al. 2017).

Various guidelines are available for the treatment of schizophrenia, i.e., NICE guidelines, PORT guidelines, IPS guidelines and so on. But in the end, all are almost the same, with little difference according to the availability of the medicine and the ethnicity. The treatment is mainly focused to treat the patients while having acute symptoms, maintenance of the improvements and preventing further relapse. All these are done step by step.

7.2 Assessment and Evaluation

First, the patients should be assessed thoroughly. Along with them, caregivers should also be assessed. History of the patient should be noted in detail, which includes demographic history, chief complaints, present illnesses, past illnesses, any medical comorbidities, the genetic connection of psychiatric and suicidal tendencies and premorbid personality. Then comes the examination part. Full physical examination should include vitals assessment and systemic examination. Then mental status examination should be performed (Grover et al. 2017).

The next step will be to establish the psychiatric diagnosis according to the current diagnostic system (DSM-5 or ICD-11) along with the severity of the illness. Also, we should look for any substance abuse, any risk of harming others, chance of self-harms and the level of adequate functioning, as all these factors need to be in consideration when choosing the medication.

Laboratory investigation also plays an important role while selecting the appropriate medication. Basic investigations which are commonly required are complete blood count, diabetes profile, liver function test, renal function test and lipid profile. Last but not least electrocardiogram like many antipsychotics affects the cardiovascular system (Taylor 2021).

Assessment of caregivers is also important as mentioned earlier. Knowledge regarding the illness, the need for medication, the course and prognosis of the illness, and what expectation caregivers have from the treatment is an important factor which will eventually lead to the cause of medication adherence (Grover et al. 2017).

If the patient is already on medications, the details of those before starting treatment need to be known.

7.3 Decision Regarding Treatment Setting

Patients can be treated at outpatient service or on an inpatient basis. Decisions should be taken as per the patient's condition and caregivers' preference. Outpatient treatment should be provided to patients whose vitals are stable. Insights regarding the illness is better for the understanding of patients, so that decision can be made with the need of the proper medications. Inpatient treatment should be preferred when a patient is aggressive, the risk for harm to self and others is present, oral input is less, and catatonia and multiple medical comorbidities are present (Grover et al. 2017).

7.4 Phases of Treatment

7.4.1 Acute Phase of Treatment

Mainly during the active phase of illness, the patients usually present with aggression, irritability, delusion, hallucinations and harm to self or others. This stage aims to control and reduce the florid symptoms (Grover et al. 2017).

7.4.2 Continuation Phase of Treatment

This phase usually lasts after the acute phase for about 6–12 months of duration. This stage aims to continue the same treatment as in the acute phase and watch for any side effects, response rate of medications or any further emergent new symptoms.

7.4.3 Maintenance Phase of Treatment

Mainly lasts about 1–2 years for the single or first episode, well response to medications; for two episodes, usually for 5 years; for multiple episodes, multiple relapses, poor response to antipsychotics longer duration or lifelong.

7.5 Options Available for Treatment

- Pharmacological management (oral/parental/long-acting injection)
- Electroconvulsive therapy
- Psychological management/non-pharmacological management

7.5.1 Pharmacological Management

Antipsychotics along with augmenting agents like antidepressants, mood stabilizers and benzodiazepines are mainly used for schizophrenia treatment.

First antipsychotic was tab Chlorpromazine which was used by Dr Henri Laborit, a surgeon who used it as an anaesthetic agent. Later found out that it has a potent effect on the psychotic disorder. Antipsychotics can be divided in two ways, one as their chemical property, one as generation and mechanism of actions.

7.5.1.1 Chemical Classification of Antipsychotic

- **Phenothiazines**
  - Aliphatic side chain—Chlorpromazine
  - Piperidine side chain—Thioridazine
  - Piperazine side chain—Trifluoperazine, Fluphenazine
- **Butyrophenones**—Haloperidol, trifluperidol, Penfluridol
- **Thioxanthenes**—Flupentixol
- **Heterocyclics**—Pimozide, Loxapine
- **Atypical antipsychotics**—Clozapine, Risperidone, Olanzapine, Quetiapine, Aripiprazole, ziprasidone.

7.5.1.2 Generation and Mechanism-Wise Classification of Antipsychotic

- **First generation (low potency)**
  Chlorpromazine, Thioridazine
- **First generation (high potency)**
  Fluphenazine, Haloperidol, Loxapine, Pimozide, Thiothixene, Trifluoperazine
- **Second generation**
  Aripiprazole, Risperidone, Clozapine, Olanzapine, Quetiapine, Lurasidone, Ziprasidone, Paliperidone, Iloperidone.

7.5.1.3 First-Generation Antipsychotics (FGAs) Mechanism of Action

As we already discussed in the previous chapter, various neurotransmitter theory is associated with schizophrenia, among them Dopamine, Glutamate and GABA Hypothesis are the main important cause.

First-generation antipsychotics which are also known as conventional antipsychotics are D2 (Dopamine receptor) antagonists (Stahl 2021). They act by lower dopaminergic neurotransmission in the four dopamine pathways. In addition to this, they can also block other receptors such as histamine-1, muscarinic-1 and alpha-1.

The dopamine hypothesis explained that postsynaptic dopamine antagonism is the common mechanism that explains antipsychotic properties (Taylor 2021).

7.5.1.4 Second-Generation Antipsychotics (SGAs) Mechanism of Action

Second-generation antipsychotics are also known as "atypical" antipsychotics or serotonin-dopamine antagonists. They are D2 (Dopamine receptor) antagonists along with 5HT2 (Serotonin) antagonists. SGAs dissociate rapidly from the D2 receptor. Affinity towards dopamine receptors for SGAs is lesser than FGAs. Some SGAs are also having 5HTA agonist properties. For example, Clozapine has a very high affinity for 5HT2A receptors and a lower D2 affinity than Haloperidol (Stahl 2021).

5HT2A antagonism helps to increase dopaminergic neurotransmission in the nigrostriatal pathway, which helps to reduce the risk of extrapyramidal symptoms. 5HT1A agonism helps to increase dopamine release in the prefrontal cortex and cause a reduction in glutamate release, i.e., ziprasidone, Quetiapine, Clozapine, etc.

FGAs and SGAs both act on the mesolimbic, mesocortical pathway, which in turn help to reduce positive and negative symptoms of schizophrenia. Through the mesocortical pathway, cognitive impairment also improved in schizophrenia.

7.5.1.5 Nobel Antipsychotic

Clozapine, due to its mechanism of action. Mainly used for treatment-resistant schizophrenia (Stahl 2021). Details of clozapine are given below:

- **Mode of action**
  - Moderate affinity for dopamine D2-receptors
  - More active at dopamine D4-receptors than other antipsychotics
  - High affinity for serotonin 5HT2A-receptors
  - High affinity for serotonin 5HT2c-receptors
  - High affinity for a1-adrenergic receptors
  - High affinity for muscarinic Mi-receptors
  - High affinity for muscarinic M4-receptors
  - High affinity for histamine H1 receptors
- **Indications**
  - The treatment of schizophrenia in patients unresponsive to, or intolerant of, conventional antipsychotic drugs; at least one drug from two chemically distinct classes should be given a full therapeutic trial before considering clozapine (the atypical antipsychotics may be used as first-line treatment of schizophrenia).
  - In addition, it may be worth considering a course of electroconvulsive therapy (ECT) before starting clozapine therapy, since this can be an effective

treatment in resistant schizophrenia (particularly when a significant affective component is present).

- **Adverse effects**
  - Less EPSE compared to conventional antipsychotics.
  - An asymptomatic rise in serum prolactin.
  - Significant weight gains due to high affinity for serotonin 5HT2C receptors; treatment-emergent diabetes mellitus does not appear to be associated with weight gain.
  - Postural hypotension with risk of collapse—therefore, treatment should be initiated with a starting dose and then gradually increased over 14–21 days to 300 mg daily in divided doses; the usual dose is 200–450 mg daily (max 900 mg daily).
  - Anticholinergic side effects: hypersalivation due to high affinity for muscarinic M4-receptors in the salivary glands is common; other atropine side effects due to muscarinic Mi-receptor blockade also occur.
  - Side effects include sedation due to the high affinity for histamine receptors.
  - Other side effects include fits and rare instances of myocarditis.
  - Some ECG changes. However, there is no requirement for routine ECG monitoring.
  - It causes agranulocytosis (life-threatening) in 2–3% of patients taking the drug—its use is therefore restricted to patients registered with the Clozaril Patient Monitoring Service (CPMS), whereby the patients have regular full blood counts to detect any possible agranulocytosis; should this occur, the clozapine must be stopped.
  - No requirement for the routine monitoring of liver function tests.
  - Requires twice daily dosing, compared to risperidone (up to 8 mg daily) and olanzapine, which require once daily dosing; this may reduce compliance in patients taking clozapine for the long-term treatment of schizophrenia (as may the requirement for regular full blood counts).

7.5.1.6 Receptor Interactions of Antipsychotics (Stahl 2021)

Three major dopamine-mediated pathways:

- Nigrostriatal (motor): substantia nigra pars compacta (A9) → striatum. D2 receptor blockade causes EPS (percentages are for typical antipsychotics)—parkinsonism (20%), akathisia (20–25%) [a pervasive sense of restlessness and an important cause of suicide], tardive dyskinesia (5%) (↑ risk with prolonged use, high dose, elderly, female; absent during sleep), dystonic reactions (10%). Dystonic reactions tend to be subjectively painful before they are clinically obvious.
- Mesolimbic [ventral tegmental area (VTA) → limbic system (amygdala, nucleus accumbens, pyriform cortex, lateral septal nucleus)] and mesocortical [VTA → septohippocampal region and frontal cortex]: perception, thinking,

emotion. Postsynaptic D2 receptor blockade responsible for clinical antipsychotic effect; ↑ VTA selectivity = ↓ EPS.
- Tuberoinfundibular (hormonal): hypothalamic arcuate nucleus (A12) → median eminence. Dopamine acts on anterior pituitary D2 receptors to suppress prolactin-release inhibiting factors. Antagonism causes hyperprolactinemia and sexual side effects: galactorrhoea, gynecomastia, amenorrhea, impotence, infertility, breast cancer and osteoporosis.

7.5.1.6.1 Effect on Other Receptors of Antipsychotics

- Adrenergic (alpha1) blockade: dose-dependent postural hypotension (particularly with phenothiazines in the elderly), necessitating careful titration when starting antipsychotics with high alpha 1 affinity (e.g., clozapine, risperidone, most typical antipsychotics). Additional effects are dizziness, tachycardia and ejaculatory failure/impotence (an important cause of non-adherence with psychotropic medication).
- Anticholinergic: central—seizures, pyrexia and possible ↓ cognitive functioning; peripheral—blurred vision, urinary retention, constipation (especially clozapine), sinus tachycardia, amnesia and reduced secretions (dry mouth). Use with caution in glaucoma and prostatism.
- Histaminergic (H1) blockade: sedation, weight gain and possibly anti-emetic effect via action on chemo-sensitive trigger zone.
- Serotonergic (5-HT) blockade: sexual disturbance (5-HT2A) and weight gain (5-HT2C). Also believed to be important in the atypical antipsychotic mechanism of action.

7.5.1.6.2 Effect on Other Systems of Antipsychotics

- Endocrine system: ↑ prolactin and melanocyte-stimulating hormone (MSH). ↓ antidiuretic hormone (ADH), adrenocorticotrophic hormone (ACTH) and possibly growth hormone (GH).
- Cardiovascular: QTc (i.e., corrected for heart rate) prolongation (>450 ms) may lead to the potentially fatal ventricular arrhythmia torsade de points. It can be linked more clearly with typical than atypical antipsychotics (particularly pimozide and thioridazine), however, ziprasidone is also implicated. The main hazards are high dose/multiple antipsychotics and pre-existing risk factors (e.g., female, elderly, electrolyte disturbance, long QT syndrome, cardiac history). In these circumstances, electrocardiogram (ECG) monitoring is advised.
- Autonomic: blood pressure and temperature regulation (dose-dependent).
- Skin: photosensitivity and allergic dermatitis (urticarial, oedematous, petechial and maculopapular). Occur early in treatment and more so with low-potency drugs. Chlorpromazine in particular can discolour the skin, especially upon exposure to the sun (necessitating sun-screen, etc. as appropriate).

- Haematological: leukopenia, agranulocytosis (incidence of 1:500,000, more likely with chlorpromazine and thioridazine), thrombocytopenia, haemolytic anaemia and leucocytosis.
- Jaundice: 1:1000. Strongly associated with phenothiazines (especially chlorpromazine and thioridazine), which cause a 'chemical' obstructive jaundice that may be part of a photosensitivity reaction.
- ↓ Seizure threshold: dose-dependent, ↑ risk the more sedative the drug. An estimated tenfold increase in seizures in non-epileptics receiving antipsychotic or antidepressant medication. Clozapine is most epileptogenic. Also recommended to avoid chlorpromazine, loxapine and depots (due to pharmacokinetics) in epilepsy.
- Eyes: irreversible pigmentation of the retina (similar to retinitis pigmentosa) seen with phenothiazines (especially thioridazine), which can lead to blindness even after treatment cessation. Deposits in the lens and cornea are not associated with changes in visual acuity. Discolouration of the conjunctiva can also happen.

7.5.1.6.3 Other Side Effects

- Emotional blunting: although this may be desirable in highly aroused individuals, it can be difficult to distinguish between apathy caused by the disease and that caused by the medication.
- Fluid regulation: up to 1/5 may drink excessively. NB: Excessive smoking can reduce urine concentration.
- Aggression: aside from possible paradoxical reactions, side effects such as akathisia may cause a medicated individual to be more irritable and impulsive.

7.5.1.6.4 Interactions

- Sedation: sedative antipsychotics likely to potentiate the sedative action of other drugs (e.g., opioid analgesics, antihistamines, alcohol, barbiturates and benzodiazepines).

EPS: ↑ risk with the contraceptive pill, opioid analgesics and psychotropic polypharmacy.

7.5.1.7 Side Effects of Antipsychotics at a Glance

- Extrapyramidal side effects
- Akathisia
- Dystonia
- Tardive dyskinesia
- Neuroleptic malignant syndrome

- ECG changes like QTc prolongation
- Ventricular fibrillation
- Orthostatic hypotension
- Hyperprolactinemia especially with SGAs
- Sexual dysfunction
- Sedation
- Dry mouth, blurring of vision

7.5.1.7.1 Tardive Dyskinesia (TD)

Affects 45–50% of patients (men and women equally) treated long-term (months to years) with antipsychotics. Risk/incidence is greatest early in treatment but increases with age and can occur in the elderly independent of antipsychotic exposure. The risk of TD is not dose-related and is not associated with the use of anticholinergic medication. The exact aetiology is unknown, but the responsible antipsychotic and any concomitant anticholinergic medication should be gradually reduced or withdrawn. Subsequent management may include clozapine, benzodiazepines, tetrabenazine and neurosurgery (pallidotomy) (Sadock et al. 2015).

7.5.1.7.2 Neuroleptic Malignant Syndrome (NMS)

- An idiosyncratic reaction (incidence up to 1%) to certain psychotropics that carries a fatality rate of up to 10%. Most commonly associated with antipsychotics (typical > atypical), but has been reported with antidepressants and mood stabilizers.
- Can occur at any stage of treatment but ↑ risk within the first 7 days (28 with the depot), high starting dose/rapid upward titration, psychotropic polypharmacy (including drugs of different classes) and concurrent systemic disease. Evolves rapidly over 3 days, lasting up to 2 weeks if untreated.

Diagnosed if all three of the following present (in someone taking a relevant medication):

- Hyperthermia (>38 °C): 're-setting' of homeostatic control + ↑ heat production secondary to muscle activity.
- Marked extrapyramidal effects: at least two of muscular rigidity, cogwheeling, oculogyric crisis, trismus, opisthotonos, sialorrhea, retro Collis, choreoathetosis movements, tremulousness or dysphagia.
- Autonomic dysfunction: at least two of tachycardia, hypertension (↑ diastolic >20 mmHg) or lability of blood pressure, urinary incontinence or marked diaphoresis.

  OR two of the above and at least one of the following:

- Fluctuating consciousness.
- Serum creatinine kinase >1000 IU/mL.
- Leukocytosis.
- Other signs include abnormal liver function tests (LFTs), hyperkalaemia, rhabdomyolysis (myoglobinuria may lead to renal damage), diffuse slowing on EEG, dehydration and proteinuria (seen in >90% of cases).

7.5.1.8 Management of NMS

- The syndrome is a serious medical emergency, and the antipsychotic must be stopped immediately.
- Bromocriptine (DA agonist) can be used to reverse anti-dopaminergic effects.
- Dantrolene can be used to relieve muscle spasms.
- If antipsychotic medication is deemed necessary post-recovery, there should be at least a 2-week interval and a structurally different antipsychotic should be used.

7.5.1.9 How to Select Antipsychotics

It is always depended upon the patient's profile. But regarding choosing the first generation vs. the second generation, most of the studies proved that there was little difference between both classes in terms of efficacy, actions, side effects and potentiality (Grover et al. 2017; Chatterjee & Mittal 2020). Some important points that should be remembered while choosing drugs are as follows:

- Cost affordability
- Severity of the symptoms
- Past treatment response
- Side effects of the medication
- Any other comorbidities like psychiatric or medical
- Patient and family preference
- Response to treatment (Table 7.1)

7.5.1.10 Selection of Route of Administration

- -For the agitated or violent patients, preferable route of administration is intramuscular injection.
- -Liquid suspension can be used for aggressive patients, non-compliance patients and children.
- -Mouth dissolving tablet can be given for non-cooperating patients, and children, when a fast onset of action is needed.
- -Oral capsule or tablet is given to most patients.

Table 7.1 Summary of dosing on antipsychotic

Antipsychotics	Daily dose (in mg/day)	Maximum dose per day
Chlorpromazine	300–800	800
Haloperidol	5–20	20
Trifluoperazine	15–30	30
Zuclopenthixol	10–50	50
Amisulpride	50–800	1200
Aripiprazole	10–30	30
Clozapine	150–600	900
Iloperidone	12–24	24
Olanzapine	10–30	30
Paliperidone	3–12	12
Quetiapine	300–800	800
Risperidone	2–8	16
Ziprasidone	80–200	200
Cariprazine	1.5–6	12

- -Long-acting injections for maintenance dose, non-compliance patients usually given monthly dose.

7.5.1.11 Long-Acting/Depot Injections Preparations

- Mode of action (Stahl 2021)
  Long-acting depot injections are administered intramuscularly as an oily injection and slowly released into the bloodstream.
- Indications
  - For maintenance therapy of schizophrenia—more conveniently given than oral antipsychotic preparations ensuring better patient compliance.
  - For prophylaxis of bipolar affective disorder in patients who have poor compliance with oral prophylactic medication (antimanic drugs)—depot medication certainly protects against hypomanic relapse, and some clinicians believe it also protects against a subsequent depressive relapse.
- Adverse effects
  - Initially, patients should always be given a test dose injection to ensure that patients do not experience undue side effects or any idiosyncratic reactions to the medication or formulation.
  - They may give rise to a higher incidence of EPSE compared to oral antipsychotic preparations.
- Available depot
  - Haloperidol decanoate 50 mg
  - Paliperidone palmitate 234 mg

- Fluphenazine decanoate 12.5–50 mg
- Olanzapine pamoate 210, 300, 405 mg
- Risperidone depot 25–50 mg

7.5.1.12 Adjunctive Medications Along with Antipsychotics

- Lithium, sodium valproate and lamotrigine are mood stabilizers usually prescribed in agitated, hyperactive patients, who have affective symptoms responding poorly to antipsychotics alone.
- Benzodiazepines like Lorazepam, Diazepam and Clonazepam are usually given for adequate sedation and to reduce agitation.
- Anticholinergic like promethazine is given to reduce the extrapyramidal side effects.

7.5.2 Electroconvulsive Therapy (ECT)

ECT can be given in all phases of treatment. In the acute phase, it is given along with antipsychotics. During the continuation and maintenance phase, maintenance ECTs can be given to the patient (Grover et al. 2017).

7.5.2.1 Mechanism of Action of ECT

- Increase permeability of blood–brain barrier which helps for better drug actions.
- Increase receptor activation from the cytoplasm.
- Changes in cerebral blood flow and regional metabolism.
- Modulates the process of neurotransmission.
- Increase brain-derived growth factors and tumour necrosis factors which are protective factors for the brain.
- Altered immune system.
- Genetic modification.
- Increase neuroplasticity.

7.5.2.2 Indications for ECT

- Suicidal behaviour
- Catatonic features
- Poor nutritional status
- Need early recovery
- Severe aggression, not manageable by antipsychotics
- Poor response to medications
- Previous good response with ECT

- Multiple side effects of antipsychotics
- Clozapine resistant schizophrenia

7.5.2.3 Number of Sessions for ECT

ECT can be given thrice weekly every week for the acute phase. Recent studies have shown that for schizophrenia up to 20 sessions are permitted. In continuation, the phase can be given according to the patient's need.

7.5.2.4 Contraindications of ECT

- Absolute contraindication only in case of raised intracranial pressure

No other absolute contraindications are there.

7.5.2.5 Relative Contraindications of ECT

- Recent stroke or intracranial haemorrhage within 3 months.
- Cardiovascular disease.
- Severe systemic hypertension.
- Huge space-occupying lesions in the brain.
- Aneurysm of brain vessels.
- Anaesthetic complications.

7.5.3 Psychological Management (Kreyenbuhl et al. 2010)

7.5.3.1 Psychoeducation for Patients and Caregivers

- Educate patient and caregivers regarding the illness
- Discuss the symptoms
- Discuss the aetiology
- Educate them regarding the course, prognosis, and outcome of schizophrenia
- Give them options regarding various modalities of treatment
- Discuss substance use or other comorbidities
- Discuss medications side effects
- Discuss caregivers' burden
- Discuss the long-term effect of medication non-adherence
- Educate them regarding plans, education, social life and marriage
- Discuss signs of relapse and seek early treatment for the same

- Improving insight regarding schizophrenia
- Discuss post schizophrenic depression and how to deal with it

7.5.3.2 Family Intervention (Grover et al. 2017)

It is mainly done in three modules. First psychoeducation, second communication skill training, and last but not least problem-solving skills.

7.5.3.2.1 Components of Family Intervention

- Teach the family about the illness
- Identify the symptoms and coarse
- Change the negative ideas regarding the illness
- Identify the stress
- Optimize family support
- Communicate effectively
- Reduce the express emotion of the family members
- Active listening
- Communication clarity
- Reduce family conflicts
- Define the family problem and divide then in into small and try to solve it by themselves

7.5.3.2.2 Advantages of Family Intervention

- Longer remission
- Reduced hospitalization rate
- Increase medication adherence
- Decrease criticism
- Reduce family burden
- Improve functional and vocational status

7.5.3.3 Cognitive Behavioural Therapy

Mainly done for ameliorating delusions and hallucinations. Patients who have some insight regarding the illness gets to benefit from this method.

7.5.3.3.1 Components of CBT

- Cognitive distortion
- Cognitive schemas
- Automated negative thoughts
- Cognitive restructuring

7.5.3.3.2 Steps of CBT

- Intake sessions
- Baseline assessment
- Goal settings
- Understanding CBT by the patient
- Thought diary
- Identify dysfunctional thoughts and cognition
- Challenging those thoughts
- Behavioural activations
- Exposure therapy
- Problem-solving
- Weaning of the sessions
- Booster session and relapse prevention

7.5.3.4 Social Skill Training

It is to improve interpersonal dysfunction that contributes to social behaviour which has been linked to individuals' isolation and interpersonal stress.

7.5.3.4.1 Components of Social Skill Training

- Social cognition
- Social competence
- Or both

7.5.3.4.2 Seven Blocks of Social Skill Training

- Social perception
- Social information processing
- Responding and sending skills
- Affiliative skills
- Instrumental role skills

- Interaction skills
- Behaviour governed by social norms

7.5.3.4.3 Commonly Used Methods

- CBT
- Role-playing
- Reality testing
- Successive approximation
- Modelling
- Positive feedback
- Reinforcement

7.5.3.5 Assertive Community Treatment

It is a community-based patient-oriented, rehabilitation-oriented model based on a multidisciplinary service team. Recommended by PORT guideline.

7.5.3.5.1 Elements of Assertive Community Treatment

- Multiple specialization teams including medical practitioner
- Sharing caseload among team members
- Direct service and treatment provision by team members
- Contact with patients is done frequently by the treating team
- Patient–staff ratio is low (10:1)
- No time limitation
- Medication delivery at home
- Mental and physical health monitoring
- Frequent contact with family members

7.5.3.5.2 Outcome of Assertive Community Treatment

- Reduce hospitalization
- Improve housing stability
- Decrease symptoms
- Increase social functioning
- Improve client and family satisfaction

7.5.3.6 Token Economy

It is a system that includes behaviour modification based on the principle of operant conditioning. It mainly emphasized reinforcing positive behaviour by giving an award "token" for improving positive behavioural goals. Patients can use this token as an exchange for privileges like watching TV or walking on the hospital campus after completing an assigned task like cleaning vessels or making their bed.

7.5.3.6.1 Advantages of Token Economy

- Tokens are always flexible.
- A token can be used for a patient's several needs.
- Desired behaviour can be an increase.

7.5.3.7 Vocational Rehabilitation

Employment rates are lower in schizophrenia patients than in general populations. Two main programs are available

- Prevocational training
- Supported employment

7.5.3.7.1 Advantages of Vocational Rehabilitation

- Employment status improves their self-esteem
- Reduce the burden on the family
- Improve medication adherence

7.6 Conclusion

A variety of options are available for the treatment of schizophrenia (Grover et al. 2017). Physician has to choose an appropriate treatment regimen according to the patient's profile and need. Including the caregivers, in the treatment protocol for schizophrenia patients, is a must for good outcomes and prognosis.

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Chapter 8
Insights into the Neuro-Pharmacological Treatment of Schizophrenia: Past, Present, and Future

Shilpa Chatterjee and Rajendra Prasad Chatterjee

8.1 Introduction

Schizophrenia and related psychoses are pervasive and devastating conditions with a prevalence rate of around 1%, frequently begins in childhood (Andreasen 1995, 1996; Carpenter and Buchanan 1994). While schizophrenic individuals may exhibit a variety of irregularities in perception, thought, language, or affect, many suffer cognitive deficits, and the majority will have significant and long-term social impairments (Green 1996). Despite much research, the illness processes and aetiology of schizophrenia remain unknown. The study of how antipsychotic medicines influence brain activity is a promising avenue of exploration into the disease's aetiology. A greater understanding of how antipsychotic medicines deliver their therapeutic effects during schizophrenia treatment can aid in the discovery of neurological pathways implicated in the disease's aetiology. The dopamine hypothesis, a popular model of schizophrenia, is the result of such an approach (Matthysse 1973). The delayed therapeutic effect of antipsychotic medications is one of the most perplexing aspects of their mode of action (Hyman and Nestler 1996). This sometimes leads to lengthy therapy trials for individuals until a drug's efficacy is established. In some circumstances, none of the currently available medications will bring about remission. The serendipitous discovery of chlorpromazine as in 1950s and the development of clozapine later in 1960s were two significant breakthroughs in the pharmacotherapy of schizophrenia (Miyamoto et al. 2008). Various

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first- (FGAs), second- (SGAs), and third-generation antipsychotics (TGAs) have been produced over the last half-century (Jarskog et al. 2007). The advancement of our understanding of neuropharmacology of schizophrenia has been aided by a considerable increase in research in the domain of pharmaceutical treatment (Biedermann and Fleischhacker 2011).

Positive symptoms are often treated with antipsychotic medicines, whereas negative symptoms or cognitive impairments are rarely treated (Conn et al. 2008; Leucht et al. 2009). These symptom dimensions are recognized as important characteristics of schizophrenia, and their paucity of treatment response correlates to impaired functional outcomes (Green 1996). Furthermore, in the vast majority of patients, positive symptoms are resilient to the existing treatments (Miyamoto et al. 2002). As a result, more effective and well-tolerated antipsychotics are urgently needed, as is the development of mechanistically innovative molecules with pharmacological action for novel targets that address the many symptom characteristics of schizophrenia. To review advances in the development of schizophrenia medicines, this article will give a complete evaluation of the pharmacology and clinical profiles of current antipsychotic medications, as well as intriguing possibilities for impending therapeutic agents.

8.1.1 Definition of Schizophrenia

Schizophrenia is a severe psychotic condition that affects several brain areas, lasts longer, and can cause social, cognitive, and maladaptive behaviors. It is the most prevalent psychosis, affecting 1% of the population. According to Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition), it is distinguished by a multitude of signs, the most prominent of which are delusions, hallucinations, thought disorder, and negative symptoms such as emotional (American Psychiatric Association 1994).

8.2 Development of Schizophrenia

Developmental abnormalities in dendritic spines are thought to be the primary source of cerebral impairment in schizophrenia (Glausier and Lewis 2013), though axonal pathology (e.g., defective myelination) could also contribute (Karlsgodt et al. 2010). As a result of a combination of genetic factors and obstetric complications, such imbalances are likely to be present from birth in some cases (Fatemi and Folsom 2009; Karlsgodt et al. 2011), but may progress beyond a critical threshold during adolescence (Weinberger 1987). Further, it can also develop in between the phase of late adolescence or early adulthood due to excessive synaptic pruning (Feinberg 1982; McGlashan and Hoffman 2000) or other aberrant processes (dendritic atrophy) (Wellman 2001; Walker et al. 2008).

8.3 Cause of Schizophrenia

There are number of factors which are directly or indirectly associated with the progression of schizophrenia which are described below.

1. **Genetic factor:** Schizophrenia is produced by a complex interplay of genetics and environmental circumstances, rather than by a single genetic mutation. If you have a close family with schizophrenia, such as a parent or sibling, your chances of having the condition are more than six times higher.
2. **Environmental factor:** It has been proven that prenatal exposure to viruses or starvation, particularly in the first and second trimesters, increases the chance of schizophrenia. A link between autoimmune illnesses and the onset of psychosis has also been discovered in recent study.
3. **Brain chemistry:** Problems with some brain chemicals and its overactivity, such as dopamine and glutamate neurotransmitters, may play a role in schizophrenia. Neurotransmitters are chemical messengers that allow brain cells to communicate with one another. Neuronal networks are also thought to be involved.
4. **Use of substance:** Taking mind-altering drugs during adolescence and young adulthood has been linked to an increased risk of schizophrenia. Also, smoking marijuana can increase the likelihood of psychotic events and chronic psychotic experiences.

8.4 Onset of Schizophrenia and Related Symptoms

Schizophrenia has been most typically diagnosed in late adolescent to early 30s, with males diagnosed earlier than females (late adolescence—early 20s). When persons initially display symptoms of schizophrenia, their first episode of psychosis is frequently followed by a diagnosis of schizophrenia. Prior to the second episode of psychosis, gradual changes in thinking, emotions, and social functioning usually occur in mid-adolescence. Schizophrenia can strike youngsters as early as 5 years old, but it is uncommon before late adolescence.

The following three categories best describe the symptoms of schizophrenia:

Psychosis is characterized by abnormal thinking, unusual behaviors, and impaired sensations (e.g., vision impairment, hearing impairment, etc.). Psychotic symptoms can cause people to lose their shared sense of reality and have distorted perceptions of themselves and the world. The following are some of the most common symptoms:

1. Perceptions of imaginary voices or objects which are not present in reality.
2. Delusions, an irrational notion or impression, that persist despite being challenged by what is commonly regarded as fact or rational argument, which is usually a sign of mental illness.
3. Unusual thinking or chaotic speech, which is a type of thought disorder.

Loss of enthusiasm, boredom, communal retreat, difficulty expressing feelings, and doing daily activities are all *negative signs*. Individuals usually have the following characteristics:

1. Low motivation, as well as difficulty planning, starting, and maintaining activities.
2. Feelings of pleasure in everyday living have dwindled.
3. "Flat affect," or a lack of emotional expression through facial expression or voice tone.
4. Simplified communication.

Cognitive symptoms include impaired memory function, attention, and concentration problems that are modest in some people, but they are more noticeable in others, interfering with activities such as following conversations, developing new skills, and remembering new things. Individuals commonly have the following symptoms:

1. Difficulty in making decisions based on information.
2. Issues with putting information to use right away after learning it.
3. Inability to focus or pay attention.

8.5 Treatments for Schizophrenia

Generally, two types of treatment currently use to treat schizophrenic patients. These are pharmacological (neuroleptics) and non-pharmacological based on the mode of treatments (Fig. 8.1). In this chapter, we have focused mainly on the neuropharmacological treatments available and what are the drawbacks to use those medications on patients. Finally, we shed light on the cutting-edge methods nowadays used as an alternative treatment to alleviate the adverse effects associated with neuroleptics.

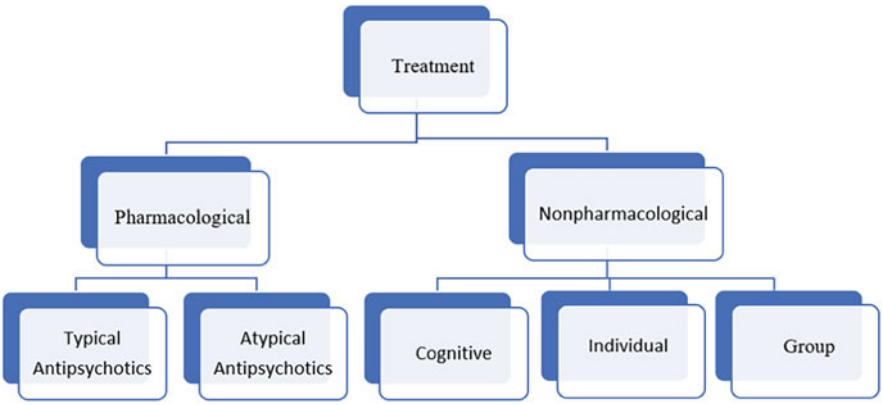

Fig. 8.1 Conventional treatment options available for schizophrenia. (Source: Crismon et al. 2014)

8.6 Neuropharmacological Treatments for Schizophrenia

8.6.1 Historical Evolution

Earlier days, the common biological therapies such as sedation, frontal lobotomy, electroconvulsive therapy, and insulin coma were used to treat psychoses. Later, the serendipitous discovery of chlorpromazine like neuroleptics replaced the era of biological therapies causing a significant shift in psychiatric practices.

Antipsychotics broadly categorized into typical (phenothiazines, butyrophenones) and atypical (benzamides) one. Followed by phenothiazine, later numerous other derivatives containing animate chain were discovered by the researcher Paul Charpentier and other. Further, the invention of "lytic cocktail" (promethazine with barbiturates) by Henri-Marie Laborit (1949) made a noticeable mark to avert surgical shock and generate pharmacological lobotomy like outcome in agitated and anxious patients (Ramachandraiah et al. 2009). It was until 1950 when a new chlorinated promazine derivative was discovered with the name of RP-4560 which was later named as chlorpromazine (López-Muñoz et al. 2005). Finally, in the year 1952, chlorpromazine was used as antimanic agent by Joseph Hammon and again in 1955 by Jean Delay as a neuroleptic agent on patient with neuroleptic syndrome. Several medications such as trifluperazine, fluphenazine became widespread after the introduction of chlorpromazine and haloperidol (Granger and Alba 2005). All were reported to be effective, but still had major neurological adverse effects including neuroleptic malignant syndrome. Thus, the quest for an alternative having fewer adverse effects continued. Eventually, clozapine, a newer tricyclic antidepressant, was synthesized in 1958 which further showed promising antipsychotic effects with no debilitating adverse effects (Grilly 2007). Clozapine remains the medicine of choice for treating refractory schizophrenia despite having additional benign side effects. Despite the fact that scientific medication research is a laborious and painstaking procedure, clozapine was effective.

8.6.2 Antipsychotic Drugs (Neuroleptics)

Antipsychotics are generally used to treat functional psychoses. In all kinds of schizophrenia, they have an intangible but obvious therapeutic effect: they relieve a wide variety of symptoms but better at regulating positive symptoms than negative symptoms. Moreover, they assist up to 90% of patients have a near-normal life in society by restoring emotional and motor abnormalities. Intelligence and cognition, on the other hand, receive minimal gain. Some patients do not respond at all, and almost none do so entirely. It is difficult to establish effective rehabilitation programs in most schizophrenia patients without the use of antipsychotic medications (Lehman et al. 2004). It is critical to begin pharmacological treatment as soon as possible after the first acute episode, especially during the first 5 years, because this

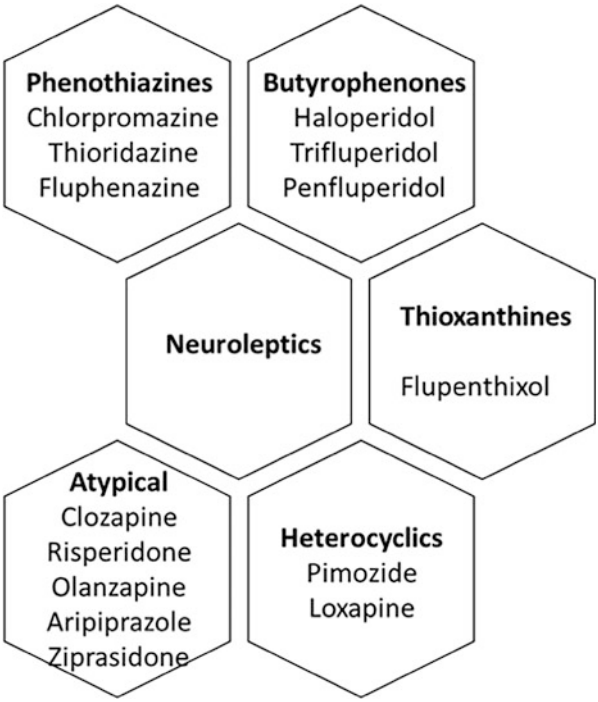

Fig. 8.2 Classification of pharmacological (neuroleptics) drugs used in schizophrenia

is when the majority of illness-related changes in the brain occur (Lehman et al. 2004; Castle and Buckley 2008).

They are simply symptomatic treatments that failed to address the underlying cause of the ailments; long-term treatment may be required. Only a small improvement in judgment, memory, and orientation can be seen. Patients who show new-onset disease symptoms and acute impaired function have a better response. The purpose of treatment is to ease symptoms and functional rehabilitation of the patient. The drug selection is essentially empirical, influenced by the observed or targeted symptoms, accompanying present state of mind, and the kind of adverse effect that is more tolerable in individual. Each patient responds differently to various antipsychotics, and it is impossible to anticipate which patient will respond better to which medicine. Based on the chemical structure and neuropharmacological action, neuroleptics are classified into typical and atypical one (Fig. 8.2).

The newer atypical antipsychotics are currently being used more frequently. Though there is no evidence of its better efficacy, shows less adverse effects and neurological issues which improve negative symptoms. Because they have a decreased risk of tardive dyskinesia, they can be used as a long-term agent in chronic schizophrenia. The high-potency ones are favored over the drugs with low potency among the older, traditional neuroleptics. Following is the comparison of adverse effects between typical and atypical antipsychotics used as a conventional treatment option for schizophrenia (Table 8.1).

Table 8.1 Comparative properties of typical and atypical antipsychotic agents (Tripathi 2013)

Drugs	Extrapyramidal	Sedative	Hypotensive
Typical antipsychotics (first generation)			
Chlorpromazine	++	+++	++
Triflupromazine	++±	+++	++
Thioridazine	+	+++	+++
Trifluoperazine	+++	+	+
Fluphenazine	+++	+	+
Haloperidol	+++	+	+
Trifluperidol	+++	+	+
Flupenthixol	+++	+	+
Pimozide	+++	+	+
Loxapine	++	+	++
Atypical antipsychotics (second generation)			
Clozapine	–	+++	+++
Risperidone	++	++	++
Olanzapine	+	+	++
Quetiapine	±	+++	++
Aripiprazole	±		
Ziprasidone	+	+	+

± minor effect; + reduced effect; ++ modest effect; +++ moderately elevated effect; ++++ elevated effect
Source: Tripathi (2013)

8.7 Mechanism of Action of Neuroleptics (Central Nervous System)

Usually, the hypothesis states that overactivity of dopamine in the limbic area and reduced expression in the prefrontal cortex contribute to the progression of schizophrenia. Thus, all neuroleptics usually function via blocking of dopamine receptor pathway. Dopamine receptors are a group of G protein-coupled receptors (GPCR) present in the central nervous system. In the year 1976, first multiple kinds of dopamine receptor subtypes were proposed (Ellenbroek et al. 2014).

At least five subtypes of dopamine receptors such as D_1, D_2, D_3, D_4, and D_5 were identified, and among them D_1, D_5 form the D_1-like group and D_2, D_3, D_4 form D_2-like family. Most antipsychotics portray its affinity towards D_2 receptor. Few drugs (phenothiazine, thioxanthene) also show D_1, D_3, and D_4 blocking activity. Blocking of over expressive dopamine receptors in the limbic area exerts antipsychotic effect by sudden increase in dopamine production followed by gradual decrease and persistent inactivation with the continuation of drug which produce therapeutic effect in schizophrenic individual. Conventionally, first-generation neuroleptics antagonise the dopamine overactivity which only regulate the positive psychotic symptoms (aggression, delusion) but not the negative one (withdrawal symptom, apathy, etc.) associated with it.

Additionally, abnormalities in other monoaminergic system such as 5-hydroxytryptamine (5-HT) and glutamate system also led to the progression of schizophrenia. Typical antipsychotics generally show the strong dopamine blocking activity but this dopamine theory failed to demonstrate the mechanism of action of atypical or second-generation neuroleptics. This class of drugs showed weak D_2 antagonistic activity along with that notable 5-HT receptor system blocking activity with some selective D_4 blocking activity.

8.7.1 Drawbacks of Traditional Neuroleptics

Based on the pharmacological actions, there are some dose-related adverse effects which vary depending on the type of neuroleptics. Both kinds of antipsychotics are widely used for a range of conditions, and both have serious side effects. First-generation antipsychotics (which are more potent D_2 antagonists) are more likely to cause D_2 receptor antagonism side effects, but second-generation (atypical) antipsychotics are more likely to cause other side effects. Nonetheless, there is a lot of variances from one medicine to the next in terms of the most common side effects. The most common adverse effects are:

1. **Extrapyramidal symptoms (EPS):** The most common dose-limiting adverse effects, which are more common in drugs with high potency such as fluphenazine, haloperidol, and other atypical antipsychotics, but are less common with drugs like thioridazine and clozapine, with the exception of higher dose risperidone. These are: Parkinsonism, Akathisia, Tardive dyskinesia, acute muscular dystonia, and malignant neuroleptic syndrome (Divac et al. 2014).
2. **Anticholinergic effects:** Blurring vision, dry mouth, urinary hesitancy, and constipation are some common side effects of high-potency typical neuroleptics.
3. **Endocrine side effects:** Due to the blockage of D_2 receptor, hyperprolactinemia (increase in prolactin level) phenomenon is also observed with typical neuroleptics and risperidone (atypical). Up to 87% of risperidone patients develop hyperprolactinemia, which can cause sexual dysfunction, decreased libido, menstrual abnormalities, and gynecomastia (Correll and Carlson 2006).
4. **Type II diabetes:** At present, elevated blood glucose and triglyceride levels due to long-term antipsychotic medication possess serious threat. Low-potency phenothiazines (chlorpromazine and thioridazine) and other SGAs, especially drugs like clozapine and olanzapine, possess high risk of exacerbating diabetes (Weiden and Ross 2002). Atypical antipsychotics including risperidone, aripiprazole, and ziprasidone, as well as high-potency medicines like trifluoperazine, fluphenazine, and haloperidol, have a low or no risk. Though the exact etiology behind this impact is unknown; it could be associated with obesity and/or an increase in resistance to insulin. Schizophrenics have a greater rate of cardiovascular death because to their increased use of atypical medication.

5. **Weight gain:** Another significant negative effect of antipsychotic medications is weight gain. It can happen in individuals with first episode of psychoses, and it can cause non-compliance (Monteleone et al. 2009; Weiden and Ross 2002).
6. **Miscellaneous:** Long-term antipsychotic medication can cause weight gain, as well as an increase in sugar and cholesterol levels. Further, phenomenon such as skin pigmentation (blue), retinal degeneration also occurs with long acting phenothiazines (at higher dose).
7. **Hypersensitivity reactions:** Though the hypersensitivity reactions are not related to drug dose, but it occurs with neuroleptics. These are: myocarditis and agranulocytosis (due to clozapine), skin rashes, dermatitis which are mainly related to chlorpromazine and in 2–4% of cases cholestatic jaundice also observed between 2 and 4 weeks of starting therapy (due to low-potency phenothiazine).

8.8 Cutting-Edge Alternatives

Symptoms related to schizophrenia may sometimes occur, but it necessitates lifelong care and medication. Due to the possible significant adverse effects associated with conventional neuroleptics, it enhances the patients' drug non-adherence rate up to 68% which further corroborate the risk of relapse. Nevertheless, there is some new hope as the number of next generation treatment options promise to reduce the likelihood of symptoms, while others showing significant efficacy with large therapeutic window which might make a long way concerning patients who suffer to maintain consistent treatment regimen. Following are the few next generation drugs and therapies available as an alternative for psychoses.

1. **Modafinil:** A cognition accelerator may be effective in treating schizophrenia's cognitive deficiency (Morein-Zamir et al. 2007). Preclinical and clinical research have shown that orthosteric and allosteric agonists of the metabotropic glutamate receptors $mGluR_2$ and $mGluR_3$ are beneficial in the treatment of schizophrenia's positive symptoms. Surprisingly, activating presynaptic $mGluR_2$ and $mGluR_3$ auto receptors lowers glutamate release, but this may be offset by an increase in NMDA receptors, which could be helpful. Targeting the dimer may offer hope for future therapeutic development because $mGluR_2$ receptors form heteromers with $5\text{-}HT_2A$ receptors with altered intracellular signalling characteristics. Agonists for post-synaptic $mGluR_5$ receptors have been shown to improve both positive and negative symptoms, as well as cognitive performance.
2. **ALKS 3831:** A promising compound combines a fixed dose of 10-mg samidorphan (potential opioid system modulator) and flexible dose of olanzapine to maintain olanzapine's proven antipsychotic efficacy while also preventing weight gain (Sun et al. 2018).
3. **Risperidone (RBP-7000):** Risperidone is one of the most commonly used monthly sustained release atypical antipsychotics for schizophrenia (Andorn

et al. 2019). The product contains two-syringe system (one contains a delivery system and other contains powdered risperidone), wherein the components are mixed directly before being administered subcutaneously into the patient's abdomen. Post-administration, it solidifies, resulting in 1-month extended release of risperidone before it biodegrades.

4. **Topical patches:** Transdermal Asenapine is a new dosage form use to treat the possible symptoms of schizophrenia (Zhou et al. 2020). The patch used as a once-daily administered formula that releases medication over 24 h in order to maintain steady-state plasma concentration. As a second-generation antipsychotic, Asenapine functions as a 5HT-2A antagonist as well as 5HT-1A/1B partial agonist that makes it an ideal candidate for treating schizophrenia yet minimizing motor side effects and enhancing mood and cognition.
5. **Aristada:** A long-acting atypical antipsychotic injectable form of medication which is a prodrug (Aripiprazole lauroxil converts to Aripiprazole upon administration) of aripiprazole (Raedler 2016). It was hypothesized that aripiprazole functions as a partial agonist as well as antagonist by targeting dopamine (D_2) and 5-hydroxytryptamine (5-HT) 1A and 5-HT2A receptors, respectively.
6. **Three neurotransmitter-pronged approach:** Lumateperone is a serotonin, dopamine, and glutamate modulator with fewer adverse effects, which shows great potency to treat schizophrenia (Correll et al. 2020). The typical antipsychotics traditionally merely modulated dopamine neurotransmission with cardiometabolic, endocrine, and extrapyramidal adverse effects, but lumateperone showed efficacy in treating negative as well as positive schizophrenia symptoms with favorable safety profile.
7. **Ulotaront (SEP-363856):** Ulotaront is an agonist at both the trace amine-associated receptor 1 (TAAR1, involved in memory, fear, attention, addiction) and the serotonin 5-HT1A receptors, making it one of the first of a new class of CNS-active chemicals (Correll et al. 2021). Unlike first- and second-generation antipsychotics, its effectiveness is not mediated by D_2 or 5-HT2A receptor blockade.
8. **Virtual reality (VR):** This is a fully computer-simulated interactive experience for an individual with psychoses in which a three-dimensional visual environment is created using a head-mounted display (HMD) (Bisso et al. 2020). Virtual reality has lately been advocated for the treatment of psychoses along with the schizophrenia spectrum. Inputs via a controller or keyboard can also be used to interact with the world, as well as tactile gloves or body motion detection techniques in the most advanced VR headsets. The motions of a subject are continuously recognized and modified in the 3D environment to give the impression of being involved in a virtual area. Currently, two types of approaches such as immersive VR (VR) and non-immersive VR (interactive VR) are used which function in a different methodological way to interact with the patients (Park et al. 2019).

8.9 Conclusion

Schizophrenia is a chronic condition that necessitates immediate treatment when symptoms of an episode of psychosis appear. When designing a thorough treatment plan, clinicians must account for the possibility of non-adherence and medicine side effects. Although present pharmaceutical and non-pharmacological therapy options can help patients improve adaptive functioning, it is hoped that future research will address treatment gaps and possibly lead to a cure for schizophrenia. Despite the fact that scientific medication research is a laborious and painstaking procedure, clozapine was successful. Several other atypical antipsychotics, such as risperidone, olanzapine, quetiapine, ziprasidone, and comparable medicines, were introduced in the 1990s. These were as effective as the other antipsychotics and had the lowest risk of extrapyramidal side effects, although they have other inherent adverse effects, such as metabolic syndrome. When we examine the effectiveness and side-effect profiles of traditional antipsychotics with atypical antipsychotics, neither appears to be preferable to the other. We have come a long way from insulin therapy and prefrontal lobotomies to antipsychotics that are not only effective but also help patients live a better life, despite some of the side effects. The hunt for a "perfect" antipsychotic medicine that addresses all facets of the condition, including positive, negative, and cognitive symptoms, continues.

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Chapter 9
Managing Schizophrenia: A Challenge for Physicians

Nimra Mumtaz and Muhammad Omair Hassan

9.1 Introduction

"Mr. Jones, an adult male was brought in by emergency services, while he was roaming around in streets seemingly looking for a space station that would take him to space. He complained of hearing voices for quite some time. He reported that he received a death call from an unknown number and believed that his life was in danger. He further complained of trouble sleeping, loss of appetite, and low mood off and on. He experienced third-person hallucinations and believed that random people on the street were insulting him. He also suffered from paranoid delusions. Upon Mental State Examination, he appeared depressed, hesitant, and shy. He was apprehensive and would not sit in the chair calmly. His insight and eye contact were poor."

Schizophrenia is a serious mental condition that leads to the distorted interpretation of reality by schizophrenic people, affecting their daily lives and social interactions. Characteristically, the clinical findings of schizophrenia have been divided into negative, positive as well as cognitive symptoms. The onset of illness is usually in the early adolescence. The constellation of symptoms with which schizophrenia presents makes it a complex syndrome with some people achieving complete remission while others following a remitting–relapsing course, qualifying for the need of chronic care (Lavretsky 2008).

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9.2 Pathomechanisms of Schizophrenia

To understand the treatment modalities of schizophrenia, a brief review of various hypotheses is necessary.

9.2.1 Dopaminergic Hypothesis

Dopamine is an inhibitory neurotransmitter, most widely implicated in pathology of schizophrenia, supported by robust research evidence. There is hyperactivity of dopaminergic pathways in mesolimbic region while the prefrontal cortex displays dopaminergic hypoactivity in schizophrenia. Other regions of brain such as amygdala, cingulate gyrus, hippocampus, and cerebellum have also been linked with dopaminergic dysregulation (Lavretsky 2008; Chatterjee et al. 2019). Dopamine receptors have been the most common target of the antipsychotic pharmacological agents. The extensive details of pathophysiology regarding involvement of dopamine are past the scope of this chapter.

9.2.2 Glutamatergic Hypothesis

Glutamate is an excitatory neurotransmitter and disturbances in signaling pathways of glutamate in mesolimbic, thalamic, and cortical regions are involved in pathology of schizophrenia, with one possible mechanism linked to hypoactivity of NMDA receptors. Glutamate is thought to be responsible for negative symptoms of schizophrenia. Cognitive symptoms might also be explained by glutamate involvement (Yang and Tsai 2017; Goff and Coyle 2001) and various antipsychotics exert their actions by modulating the activity of glutamate receptors.

9.2.3 Other Aminergic Receptors

Besides dopamine, other aminergic receptors such as serotonin, muscarinic, histamine, oxytocin, and adrenergic receptors have been linked with the pathophysiology of schizophrenia and clinical trials are underway to further explore these receptors as drug targets (Lavretsky 2008; Bansal and Chatterjee 2021).

9.2.4 GABAergic Hypothesis

Gamma-aminobutyric acid (GABA) is the chief inhibitory neurotransmitter involved in repression of central nervous system (CNS). GABA also plays key role in memory and cognition (Bansal and Chatterjee 2021), but the mechanism by which it can lead to schizophrenia is still unclear and warrants further research.

9.2.5 Other Hypotheses

Ongoing research indicates the possible role of nicotinic receptors, endocannabinoid system, and oxidative stress in pathology of schizophrenia (Wallace and Bertrand 2015; Fernandez-Espejo et al. 2009; Watkins and Andrews 2016) with novel drug targets being studied.

9.3 Clinical Management of Schizophrenia

The management of schizophrenia has been tricky since the introduction of the illness because of the complexity of diagnosis. The diagnosis of schizophrenia is mostly clinical but advances in neuroscience are helping in bridging the gap (Chatterjee et al. 2018).

When managing schizophrenic patients, the main goals are to enhance the patients' quality of life while limiting the debilitating effects of the condition. Complete cure of schizophrenia is not possible currently and the management is mostly centered around increasing the functional level of the patients and restoring their social interactions to near-optimum level.

Broadly, the management of schizophrenia can be divided into two categories:

1. Pharmacotherapy
2. Psychotherapy

9.3.1 Pharmacotherapy

Antipsychotics are the mainstay of clinical treatment of schizophrenia since their discovery. These drugs act on dopamine receptors. Antipsychotics are more commonly classified into "First-Generation" aka "Typical" antipsychotics and "Second-Generation" aka "Atypical" antipsychotics (Chatterjee and Mittal 2020). Since then, "Third-Generation" antipsychotics have been introduced as well (Shapiro et al. 2003).

9.3.1.1 First-Generation Antipsychotics (FGAs)

The first-generation antipsychotics are called the typical antipsychotics because of the extrapyramidal side effects that lead to Parkinson-like syndrome in schizophrenic patients being treated with these drugs. FGAs are also called neuroleptics and can cause neuroleptic syndrome characterized by cognitive dullness, restricted range of emotion, and lack of motivation.

Mechanism of Action

The first-generation antipsychotics are mainly non-selective dopamine D2 receptor antagonists. These drugs lead to hypoactivity of dopaminergic neurons in number of pathways with major pathways being mesolimbic, mesocortical, nigrostriatal, and tuberoinfundibular. The inhibition of dopamine receptors in the mesolimbic pathway is suggested to ameliorate the positive symptoms of schizophrenia. Likewise, the negative symptoms seem to worsen with the simultaneous blockade of dopamine receptors in mesocortical pathways.

Adverse Effects Profile

The non-selectivity of FGAs is the main cause of major extrapyramidal Parkinson-like side effects associated with hypoactivity of dopaminergic neurons in nigrostriatal pathway categorized as acute dystonia and tardive dyskinesia. Non-selective dopamine blockade in different parts of the brain leads to other side effects such as hyperprolactinemia, drowsiness, sedation, dementia, and insomnia. Dopamine blockade also seems to affect various organ systems with chief effects on cardiovascular system. Gastrointestinal disturbances and genitourinary side effects have also been reported frequently (Ritter et al. 2020).

The advent of chlorpromazine, the first antipsychotic medication, formed the core of the dopaminergic hypothesis in the pathomechanism of schizophrenia. Since then, several antipsychotics have been discovered: among them, some examples of first-generation antipsychotics are as follows:

- Chlorpromazine
- Prochlorperazine
- Fluphenazine
- Fluspirilene
- Thiothixene
- Pimozide
- Haloperidol

Chlorpromazine Equivalent Dose

Chlorpromazine (CPZ) equivalent dose is defined as the dose of an antipsychotic drug whose potency is comparable to 100 mg of chlorpromazine. Traditionally, CPZ equivalent dose method is employed to calculate dosages of antipsychotics mainly the FGAs. This method guides clinicians in switching patients from one antipsychotic to another. With the discovery of second-generation antipsychotics, the preferrable method to calculate drug dose is defined daily dose (DDD) (Lin et al. 2018). The World Health Organization (WHO) devised DDD, which is expressed as "the assumed average maintenance dose per day for a drug used for its main indication in adults" (WHOCC 2018).

Over the years, second-generation antipsychotics have mostly supplanted first-generation antipsychotics due to their side effect profile; however, the FGAs are still commonly prescribed due to their affordability and availability.

9.3.1.2 Second-Generation Antipsychotics (SGAs)

The second-generation antipsychotics are also called the atypical antipsychotics because of relative lack of extrapyramidal symptoms associated with the first-generation antipsychotics. These drugs are generally considered to be the "First-line drugs" against schizophrenia. The first SGA to be discovered was clozapine, since then there have been several SGAs approved for clinical use.

Mechanism of Action

The SGAs exert their effects by blockade of both dopamine D2 and serotonin $5HT_{2A}$ receptors, more so at serotonin than dopamine receptors. Their property of acting at different receptors from dopamine receptors attributes them with a safer side effects profile as compared to the first-generation antipsychotics, hence the term "Atypical" antipsychotics.

Among the most widely used second-generation antipsychotics are as follows:

- Clozapine
- Olanzapine
- Quetiapine
- Risperidone
- Paliperidone
- Ziprasidone
- Molindone

Clozapine: The Most Atypical Antipsychotic

Clozapine, specifically, exerts its effect by blocking both serotonin and dopamine D4 receptors, believed to account for the relief of negative symptoms. Clozapine has an advantage over FGAs in that it has fewer extrapyramidal side effects when administered. This effect of clozapine is due to more affinity of clozapine for D4 and 5-HT_2 receptors than D2 receptors, which are responsible for extrapyramidal side effects. Clozapine is further unique in its pharmacological profile with action at various receptors other than dopamine and serotonin namely, muscarinic receptors, histamine receptors, and α_1-adrenergic receptors (Ritter et al. 2020). Clozapine has also been reported to be a partial agonist at the serotonin 5-HT_{1A} receptor, and improvements in negative and cognitive symptoms of schizophrenia have been linked to this property (Aringhieri et al. 2018).

Although clozapine and structurally related olanzapine have less extrapyramidal side effects, clozapine is notorious for causing agranulocytosis, prompting clinicians to monitor the white cell count of schizophrenic patients being treated with clozapine. Olanzapine does not cause agranulocytosis but has been associated with sedation and weight gain (Ritter et al. 2020).

9.3.1.3 Treatment-Resistant Schizophrenia

Clozapine causes agranulocytosis and may cause death of the patients taking this drug, so routine use of clozapine as the first-line drug is no longer recommended. Instead, clozapine has been reserved for management of treatment-resistant schizophrenia. So, when do we label a schizophrenic patient to be treatment-resistant?

A schizophrenic person is said to be treatment-resistant if he/she has persistence of schizophrenic symptoms despite two or more than two antipsychotic drug trials with standard dose, appropriate interval, and documented compliancy with drug therapy, excluding other reasons of drug failure. Clozapine has been shown to have the greatest efficacy in controlling treatment-resistant schizophrenia as compared to other antipsychotics (Howes et al. 2017).

According to APA clinical practice guidelines, clozapine has also been indicated in schizophrenia patients with increased risk of suicide or suicide attempts and aggressive behavior, not responding to other therapy (Keepers et al. 2021).

Risperidone

After clozapine, the first second-generation antipsychotic to be developed was risperidone, fundamentally for schizophrenia. Risperidone acts as blocker at both serotonin 5-HT_2 and dopamine D2 receptors. When compared to conventional first-generation antipsychotics, risperidone has the advantage of improving positive as well as negative symptoms of schizophrenia while causing minimal extrapyramidal side effects. These advantages extend to having better tolerability as well. There has

been evidence to suggest that risperidone might also improve the cognitive symptoms of schizophrenia. As compared to other SGAs, risperidone has more favorable adverse effects profile with less weight gain and endocrine abnormalities (Möller 2005).

Adverse Effects Profile

No antipsychotic is completely free of extrapyramidal side effects, but SGAs have shown less of these extrapyramidal side effects than FGAs. At therapeutic doses, side effects of SGAs include sedation, weight gain, cognitive dullness, cardiometabolic dysfunction, hypotension, gastrointestinal side effects, genitourinary problems, agranulocytosis, leucopenia, thrombocytopenia, osteoporosis, behavioral issues, impulsivity, smoking tendencies, diabetes, hyperprolactinemia, and neuroleptic malignant syndrome. There may be withdrawal and rebound syndromes associated with long-term usage of antipsychotic drugs (Solmi et al. 2017).

9.3.1.4 Third-Generation Antipsychotics

Aripiprazole, brexpiprazole, and cariprazine are the newest generation of antipsychotics. Since their mechanism of action, like previous antipsychotics, is via dopamine and serotonin receptor system so their classification as the third-generation antipsychotics is the subject of debate among researchers.

Mechanism of Action

These third-generation antipsychotics as opposed to FGAs and SGAs are the partial agonists at D2 dopamine receptors in the brain. Aripiprazole is the first third-generation antipsychotic to be approved for schizophrenia. Aripiprazole is a partial agonist at serotonin 5-HT_{1A} and 5-HT_{2A} receptors with additional activity at D2 receptors, but its affinity for dopamine receptors is much stronger than that of serotonin receptors. Aripiprazole has shown better or comparable results in improving symptoms of schizophrenia as compared to the FGAs and the SGAs with additional advantage of better tolerability (Leucht et al. 2013).

Adverse Effects Profile

Adverse effects of aripiprazole are like other antipsychotics that include weight gain, sedation, akathisia, insomnia, and gastrointestinal side effects. However, these side effects are considerably lower when compared to other antipsychotics mainly risperidone, clozapine, olanzapine, and typical antipsychotics (Ribeiro et al. 2018).

It is necessary to understand the mechanisms of various antipsychotics for schizophrenia, keeping an eye out for the development of adverse effects of these antipsychotic drugs. The patients' tolerability must guide the choice of antipsychotic in treatment regimen (Schimmelmann et al. 2013).

Table 9.1 provides a brief overview of the side effects of selected antipsychotics, adapted from Kahn et al. 2015.

Antipsychotics are primarily useful in alleviating positive symptomatology of schizophrenia, while negative and cognitive symptoms of the illness continue to pose difficulties for treating clinicians. Further research and drug trials are needed to develop targeted therapies while more understanding of the underlying mechanisms is achieved (Kahn et al. 2015).

9.3.2 Non-pharmacotherapy

Although the mainstay of management of schizophrenia has been antipsychotic drug therapy, non-pharmacotherapeutic approaches play an essential role in maintaining remission, preventing relapse, and improving the functional outcomes of schizophrenia patients. There are various options for non-pharmacological management of schizophrenia (Kahn et al. 2015; Dickerson and Lehman 2011).

1. Psychotherapy
2. Electroconvulsive therapy
3. Transcranial magnetic stimulation therapy

9.3.2.1 Psychotherapy

Psychotherapy is defined as "an interpersonal process designed to bring about modifications of feelings, cognitions, attitudes, and behaviour which have proven troublesome to the person seeking help from a trained professional" (Dickerson and Lehman 2011).

Some of the main psychotherapeutic approaches are shown in Fig. 9.1, adapted from Crismon et al. 2014.

The different forms of psychotherapy include the following:

- Cognitive Behavioral Psychotherapy (CBT)
- Compliance Therapy
- Personal Therapy
- Acceptance and Commitment Therapy
- Metacognitive Therapy
- Narrative Therapy
- Supportive Therapy
- Mindfulness Therapy

Table 9.1 Side effects of some selected antipsychotic drugs

	First-generation antipsychotics			Second-generation antipsychotics					Third-generation antipsychotics	
Adverse effect	CPZ	HAL	PER	CLO	OLA	RIS	ZIP	QUE	ARI	Underlying mechanism
Anticholinergic effects	++	0	0/+	+++	++	0	0	+/++	0	Muscarinic acetylcholine receptor blockade
Acute Parkinson-like side effects	+	+++	++	0	0/+	++	+	0	+	Dopamine receptor blockade primarily D2
Akathisia	+	+++	++	+	+	+	+/++	+	++	Dopamine D2 receptor antagonism (?) and Dopaminergic and serotonergic/noradrenergic neurotransmitter systems imbalance (?)
Cerebrovascular side effects	+?	+?	+?	+?	+	+	+?	+	+	Hypercoagulability mediated by D2 receptors (?)
Diabetes mellitus	+++	0/+	+	+++	+++	+	0/+	++	0/+	Obesity and direct effects (?)
Hyperlipidemia	+++	0/+	+	+++	+++	+	0/+	++	0/+	Obesity and direct effects (?)
Neutropenia	0	0	0	++	0	0	0	0	0	Unknown
Overproduction of saliva	0/+	0/+	0/+	++	0/+	0/+	0/+	0/+	0/+	Muscarinic acetylcholine M4 receptor
Orthostatic Hypotension	++	0	+	+++	++	+	0	+++	0/+	α1-Adrenergic receptor antagonism
Hyperprolactinemia and sexual dysfunction	+	++/+++	++	0	+	+++	+	0	0	Dopamine D2 receptor antagonism
Decreased prolactin	0	0	0	0	0	0	0	0	+	Dopamine D2 receptor activation leading to high levels of dopamine
Prolonged QTc interval	0/+	0+	+	+	0/+	+	++	+	0/+	Ion channel changes in heart
Sedation	++	+	+	+++	+/++	+	+	++	0/+	Histamine H1 receptor antagonism
Seizures	0/+	0/+	0/+	++	0/+	0/+	0/+	0/+	0/+	Dopamine D2 receptor antagonism (?)
Tardive dyskinesias	++	++	++	0	0/+	0/+	0/+	0/+	0/+	Unknown
	0/+	++		0	0/+	+	+	0/+	+/++	Dopamine D2 receptor antagonism rebound

(continued)

Table 9.1 (continued)

	First-generation antipsychotics			Second-generation antipsychotics					Third-generation antipsychotics	
Adverse effect	CPZ	HAL	PER	CLO	OLA	RIS	ZIP	QUE	ARI	Underlying mechanism
Withdrawal, dyskinesia			+/++							
Weight gain	+++	+	++	+++	+++	++	0/+	++	0/+	Histamine H1 receptor antagonism (?), serotonin 5-hydroxytryptamine 2C (5-HT2C) receptor blockade and dopamine D2 receptor blockade (?)

0 indicates absent; + indicates mild; ++ indicates moderate; +++ indicates marked; ? indicates questionable. CPZ for chlorpromazine, HAL for haloperidol, PER for perphenazine, CLO for clozapine, OLA for olanzapine, RIS for risperidone, ZIP for ziprasidone, QUE for quetiapine, ARI for aripiprazole

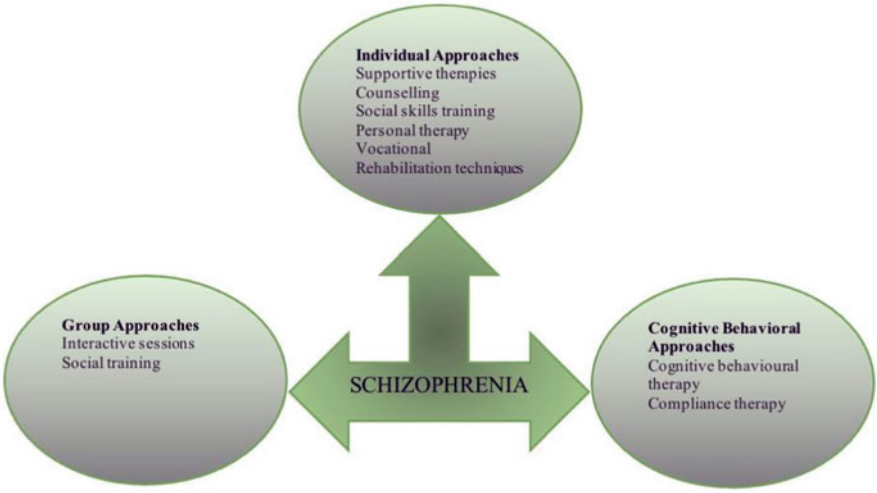

Fig. 9.1 Main psychotherapeutic approaches

Psychotherapy has been shown to be efficient in achieving remission and enhancing the quality of life of patients with schizophrenia. Patients receiving psychotherapy are more likely to achieve better functionality in their social lives (Dickerson and Lehman 2011).

Cognitive Behavioral Therapy

Traditionally, cognitive behavioral therapy has been used to treat major psychiatric disorders such as depression and anxiety (Lynch et al. 2009). The CBT has gained much popularity over the years for management of schizophrenia as well. Although pharmacotherapy for schizophrenia can assist in resolution of positive symptoms, persistence of negative symptoms remains a challenge for the clinicians. CBT can be employed to aim at the negative symptoms of schizophrenia that persist despite optimum antipsychotic therapy (Rector and Beck Aaron 2001). Table 9.2 describes some techniques employed for CBT, adapted from Morrison (2009).

9.3.2.2 Electroconvulsive Therapy

Electroconvulsive therapy (ECT) can be an option for treatment of schizophrenia not responding to antipsychotic drug trials. It entails applying electrical electrodes to the top of the head and inducing therapeutic electric shock by delivering a variable frequency electrical stimulus. Electroconvulsive therapy can be given alone or combined with antipsychotic drugs. However, the data on ECT as individual treatment modality of schizophrenia are insufficient (Tharyan and Adams 2005).

Table 9.2 Cognitive behavioral therapy for schizophrenia

Objective	Approach	Description
Positive symptoms	Alternative explanation	This technique helps patients to generate alternatives to substitute previous maladaptive beliefs.
Hallucinations	Normalizing techniques	These techniques help influence the patients about how they think about and react to certain situations.
	Improving coping techniques	
Delusions	Inference chaining	These techniques help patients in dissecting their delusions with unraveling of the links that lead them to realize the falsehood.
	Peripheral questioning in conjunction with reality testing	
Negative symptoms	Behavioral experimenting	These interventions help modify the problematic thoughts and resulting behavior patterns.
Avolition	Self-monitoring therapies	These techniques involve graded approach to ameliorate the negative symptoms by targeting specific behavior patterns.
Anhedonia	Mastery and pleasure recordings	
Asociality	Behavioral activation	
Affective flattening	Social skills training	

9.3.2.3 Transcranial Magnetic Stimulation Therapy

Repetitive transcranial magnetic stimulation therapy (rTMS) involves the stimulation of different brain areas by electromagnetic stimuli. It has shown mixed results in improving the negative symptoms of schizophrenia. More research is needed to investigate the effects of rTMS on negative schizophrenia symptoms before it can be considered a potential treatment (Dlabač-de Lange et al. 2010).

9.4 Augmentation Strategies

Augmentation strategies are employed in schizophrenia patients in whom drug treatment has failed or refused by the patient. Patients not responding to clozapine are offered augmentation therapy since amelioration of symptoms remains the primary goal. Augmentation strategies include the addition of drugs besides antipsychotics to provide symptomatic relief and improving the quality of life. Aspirin, omega-3 fatty acids, antidepressants, NMDA agonists, nicotinic receptor agonists have shown somewhat mixed results when administered with antipsychotic drugs in symptomatology of schizophrenia (Kahn et al. 2015; Kane et al. 2003).

9.5 Phase-Wise Management of Schizophrenia

Patients with schizophrenia can present in different phases of their mental illness. The illness may begin with a period of ill-defined symptoms followed by an interval in which patients are at greater risk of experiencing full-blown schizophrenia. The condition may progress when patients experience their first episode of psychosis, after which they might seek treatment. The patients may go into remission with treatment, or their symptoms might persist after treatment and eventually develop resistance against antipsychotic drugs (McGorry et al. 2018).

9.5.1 Management of First-Episode Psychosis

Patients experiencing their first episode of psychosis might present with hallucinations, delusions, or social withdrawal. Patients often present to their clinicians later than the onset of symptoms, and their condition remains undiagnosed for variable intervals of time. Efforts should be made to reduce this duration of undiagnosed psychosis (DUP) as early treatment of first-episode psychosis provides opportunities for effective recovery. Treatment options include the following:

9.5.1.1 Psychotherapy

- Cognitive behavioral therapy—CBT assists patients with schizophrenia in handling their presenting issues. The therapist assists the patient with figuring out how to perceive and change mistaken convictions, distinguish contorted reasoning, change risky behaviors, and connect with others in additional positive ways.
- Family therapy—Education of family members about psychosis helps in better adaptive response and patients feel more supported and motivated during recovery process.

9.5.1.2 Pharmacotherapy

Antipsychotic drugs are initiated in patients presenting with first episode of psychosis. Although treatment with antipsychotics should continue for longer periods of time since relapses are very frequent in patients with schizophrenia, the drugs are generally discontinued after 1–2 years owing to several factors: side effects of the antipsychotic therapy, non-adherence to the therapy, non-compliance of the patients, financial affordability, etc. (Fusar-Poli et al. 2017).

According to APA clinical practice guidelines, patients presenting with their first episode of psychosis should be started on minimum dosage of antipsychotic drug. The choice of antipsychotic drug becomes difficult with discrepancies in clinical

trials regarding the efficacy of antipsychotic drugs in different clinical scenarios. The best course of action would be to involve patients and, when possible, their families in deciding upon the management plan of the illness. After patients have been informed about the side effects associated with different antipsychotic drugs and the likely benefits of the therapy, the selection of antipsychotic therapy should be centered on their preferences, as well as their individual presentation and therapeutic goals. Generally, SGAs are preferred over FGAs with their less extrapyramidal side effects. Antipsychotics are available in different formulations. Depending on individual circumstances, different formulations are chosen in different patients. For instance, patients with known non-compliance or possible non-compliance should be offered long-acting injectables (LAI) instead of oral therapy (Keepers et al. 2021).

9.5.2 Management of Acute Phase

If acute relapses occur in a patient with previous diagnosis of schizophrenia, the likely underlying cause should be investigated after the initial management. If the patient presents with an acute episode of psychosis, initiation of antipsychotic therapy should be prioritized. Antipsychotic medications might take a couple of weeks to produce clinically visible response in the patients, thus making it necessary to carefully adjust and monitor the levels of antipsychotic drug while correlating with the clinical response.

Antipsychotic monotherapy is recommended by most clinical practice guidelines, started at the lowest effective dose. If the patient does not tolerate the initial monotherapy or provide the evidence of efficacy, trial of another single antipsychotic should be offered (Correll et al. 2022).

The choice of antipsychotic in acute phase depends upon various factors that include patient's history of previous antipsychotic therapy and preference of patients for a particular drug or drug formulation. Patients might be reluctant to take antipsychotic medication with less favorable adverse effect profile, leading to non-adherence. Non-adherence might be one of the reasons behind acute relapses in the patients taking antipsychotic therapy along with substance abuse and criticism of the caregiver (Alvarez-Jimenez et al. 2012).

After starting treatment during the first week, the objective is to endeavor to restore patient's functioning to normal or near normal and curb aggressive behaviors. If schizophrenia symptoms do not improve despite antipsychotic therapy for 2–4 weeks, the patient is most likely not going to respond to that antipsychotic drug. Clozapine should be started if the patient meets the criteria for treatment-resistant schizophrenia (Crismon et al. 2014; Keepers et al. 2021).

Along with pharmacotherapy, psychotherapy should be offered to patients presenting with acute relapse of schizophrenia symptoms. Although CBT was fundamentally developed to address the persistence of schizophrenia symptoms, some evidence suggests that CBT is also effective in preventing relapse at 1 year after first-episode psychosis (Bighelli et al. 2021). Family interventions and family

psychoeducation have been especially found to be very advantageous in reducing the hospitalization rates, preventing future relapses, and treating current episode by ensuring better adherence to the drug therapy, and encouraging effective recovery in schizophrenia patients (Rodolico et al. 2022).

9.6 Maintenance Phase of Schizophrenia

After the acute relapse in a schizophrenia patient has been managed, the patient should be started on maintenance therapy. Antipsychotics have been proven to be efficacious in preventing future relapses. However, the data are insufficient to indicate the duration of antipsychotic treatment, with most studies depicting the continuation of antipsychotic therapy up to 1 year. Since antipsychotic therapy is associated with several side effects, patients' choice should be considered. Evidence indicates that in the maintenance phase, antipsychotic therapy has been linked to improved quality of life and functional outcomes (Ceraso et al. 2020).

For first-episode psychosis patients with schizophrenia, recommendation is to continue maintenance therapy for 1 year while multiple-episode patients should be continued on maintenance therapy for 5 years. The choice of antipsychotic mainly depends on patients' preference and tolerability as there is no robust evidence for superiority of any antipsychotic drug over another (Schneider-Thoma et al. 2022); therefore, an additional considerable point when prescribing drugs for maintenance should be patients' response to antipsychotic therapy in the acute phase. If benefits outweigh the side effects, patients can be kept on the antipsychotic drug to which they have shown positive clinical response in the acute phase (Leucht et al. 2011). Among psychotherapeutic approaches, CBT is proven to be the most effective in preventing relapse and reducing hospitalization and should be the psychotherapeutic modality of choice in schizophrenia patients (García Valencia et al. 2014).

Another important aspect to consider while treating patients with schizophrenia is to clearly elucidate patients' clinical history. This provides clue to the co-morbid conditions, affecting the prognosis of pharmacotherapy of schizophrenia. Patients with schizophrenia might have other concurrent psychiatric illnesses such as major depressive disorder, post-traumatic stress disorder (PTSD), and anxiety disorders. These conditions might also result from the institution of antipsychotic therapy as well, thus making it necessary for the clinicians to consider changing drug regimens or introducing new drugs depending on patients' clinical condition. Patients with schizophrenia might also be suffering from substance-abuse disorders and nicotine dependence (Keepers et al. 2021).

9.7 Dosing Regimens for Antipsychotics

Different clinical practice guidelines recommend slightly different dosing regimens; however, there is consensus on initiation of antipsychotic therapy at the lowest possible dose with proven efficacy. Dose of the drug should be increased by gauging the patient's response to that drug. Adverse effects of antipsychotics are minimum at low doses, thus prompting clinicians to carefully evaluate patients with schizophrenia to ensure maximum adherence and minimum side effects (Correll et al. 2022). Table 9.3 includes doses of some antipsychotics taken from APA clinical practice guidelines for some selected antipsychotics, adapted from Keepers et al. (2021).

9.8 Antipsychotics in Pregnancy

There has not been much difference noted in pregnancy rates among normal women and women with schizophrenia (Howard et al. 2001). This fact necessitates the need to address the management of schizophrenia in pregnancy, but due to ethical reasons, clinical trials involving pregnant women are seldom undertaken with most of the data being provided by case reports and observational studies (Desai and Chandra 2009). Pregnant women with schizophrenia are more likely to have antenatal, obstetric, and postpartum complications, therefore making it imperative to treat any psychotic episode during pregnancy (Howard 2005). Both clinicians and mothers with schizophrenia are generally cautious about antipsychotic therapy in pregnancy (Trixler et al. 2005) as it is well known that antipsychotic drugs can cross the placental barrier and enter fetal circulation. Drug metabolism and clearance also

Table 9.3 Doses of some selected antipsychotics

Antipsychotic medication	Starting dose (mg/day)	Average dose range (mg/day)	Maximal dose per day (mg/day)
Chlorpromazine	25–100	200–800	Oral: 1000–2000
			IM: 200
Haloperidol	1–15	5–20	Oral: 100
			IM: 20
Perphenazine	8–16	8–32	64
Clozapine	12.5–25	300–450	900
Olanzapine	5–10	10–20	20
Risperidone	2	2–8	8
Ziprasidone	40	80–160	320
Quetiapine	Immediate release: 50	400–800	800
	Extended release: 300		
Aripiprazole	10–15	10–15	30

undergo modification in pregnancy, which may lead to lower-than-required drug levels to keep the patient in remission (Goldberg and Nissim 1994).

Despite the risk of antipsychotic drugs crossing the placenta, evidence indicates that keeping the psychotic mother untreated during pregnancy leads to more harm than benefits (Howard 2005). Antipsychotics are most used by women in pre-pregnancy period and during first trimester, with their use decreasing in second and third trimesters as the risk of teratogenicity and fetal toxicity increases during organogenesis (Reutfors et al. 2020). All the antipsychotic drugs are labeled as category "C" according to the United States Food and Drug Administration (FDA) with the exception of clozapine, which is labeled as category "B." Atypical antipsychotics are generally preferred due to their less adverse effects. Pregnant women with schizophrenia must be provided with excellent prenatal and postnatal care due to high risk of complications related to the disease process as well as the antipsychotic treatment (Armstrong 2008). Quetiapine, aripiprazole, risperidone, and olanzapine are the most frequently used antipsychotics in pregnant women with schizophrenia. There appears to be no serious risk of congenital malformations associated with these drugs (Betcher et al. 2019), but due to limited data availability, it is advisable to weigh risk against benefits.

9.9 Antipsychotic Withdrawal

Patients with chronic or relapsing schizophrenia require antipsychotic medication for extended periods of time, which translates into more incidence of side effects and secondary symptoms due to drug therapy (Sabe et al. 2021). Literature indicates that protracted antipsychotic therapy does not reduce the risk of relapse significantly; therefore, dose reduction strategies must be employed to reduce the incidence of side effects. Tardive dyskinesia is the most serious side effect associated with extended antipsychotic therapy, negatively affecting the quality of schizophrenia patient's life and functional status. Rest of the extrapyramidal side effects further complicate the status of schizophrenia patient over prolonged periods. Despite the high risk of serious side effects caused by prolonged antipsychotic therapy, not all schizophrenia patients respond to dose reduction strategies (Schooler 1991). Since complete cure of schizophrenia is not possible with the use of antipsychotic therapy, patients and clinicians might not want to continue pharmacological treatment due to side effects of antipsychotics. Although it seems a logical option in stable schizophrenia patients, evidence shows that the risk of relapse of schizophrenia symptoms becomes high with withdrawal of antipsychotics (Atkinson et al. 2007). These symptoms occur more commonly after abrupt cessation of antipsychotic therapy (Brandt et al. 2020) There is paucity of research data to show whether antipsychotics should be maintained in chronic schizophrenia patients or withdrawn to save the patient from serious side effects such as tardive dyskinesia, instead putting them at the risk of a psychotic relapse. Therefore, antipsychotic withdrawal remains an issue that needs to be handled while weighing the risks against the benefits (Gilbert et al. 1995).

9.9.1 Neuroleptic Malignant Syndrome (NMS)

Exposure to dopamine antagonists or sudden cessation of dopamine agonists may lead to neuroleptic malignant syndrome. This clinical syndrome can be rapidly fatal, if unrecognized and untreated. Essentially, all the antipsychotics can potentially cause NMS. NMS is considered a diagnosis of exclusion. The complexity of diagnosis of NMS arises from the fact that it can be caused by other medical conditions as well, prompting the clinicians to keep high index of suspicion (Ware et al. 2018). The diagnostic features of NMS include hyperthermia, autonomic instability, altered state of consciousness, and muscle rigidity (Tse et al. 2015).

Clinical management of NMS involves supportive care and discontinuation of the offending drug. Benzodiazepines can be administered to provide relief from muscle rigidity; however, caution is needed as benzodiazepines can lead to respiratory depression, further aggravating the condition. Dantrolene, bromocriptine, and dopamine agonists can be considered as other pharmacological options for lowering body temperature and reducing muscle rigidity (Velamoor 2017). Another treatment option gaining popularity over the years is electroconvulsive therapy. ECT has been demonstrated to be the most efficacious treatment in lowering NMS-related mortality (Kuhlwilm et al. 2020).

9.10 Future Research Recommendations

There is no complete cure for schizophrenia currently. Side effect profile of antipsychotics limits their clinical utility. Further drug trials are needed to develop drugs with more favorable side effect profile. Negative and cognitive symptoms of schizophrenia are more resistant to treatment and efforts need to be directed to target these symptoms (Köster et al. 2014). Moreover, research is needed to develop targeted psychotherapeutic techniques to cope with the symptoms of schizophrenia as well as to improve the functional outcomes of schizophrenia patients and incorporate them in clinical management of schizophrenia. It is important to introduce novel psychotherapies and relinquish the orthodox approach toward psychotherapy that stands as a barrier between researchers and clinical care providers (Gaebel and Zielasek 2015). Emerging neuroimaging modalities are also providing valuable information about etiopathogenesis and prediction of outcomes in schizophrenia patients (Keshavan et al. 2020). Integration of diagnostic modalities with targeted treatment models might become the breakthrough needed in tackling this complex mental disorder.

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Chapter 10
Pharmacotherapy and Emerging Treatment Strategies for Schizophrenia

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10.1 Introduction

Schizophrenia (ScZ) is a chronic and heterogeneous psychiatric illness that disrupts numerous cognitive functions, like learning, memory, perception, thought pattern, decision-making, etc. It is a detrimental disorder that affects 0.5–1% population globally (Freedman 2003). The two scientists, Kraepelin from Germany and Bleuler from Switzerland, recognized consistent patterns of signs that emerged together in clinical settings at the start of the twentieth century, coining the name "schizophrenia" (Maric et al. 2016). These symptom patterns were thoroughly investigated, and numerous multidimensional models were discovered.

Even though the classification of ScZ as a single disorder was maintained in the International Classification of Diseases and Diagnostic and Statistical Manual during

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the twentieth century, there is widespread agreement that ScZ has at least three dimensions of symptoms (core features): negative symptoms (trouble speaking, lack motivation, diminished interest in socializing, poverty of spontaneous movement), positive symptoms (difficulty concentrating, delusions, hallucinations, impaired thoughts, movement disorder), and cognitive symptoms (memory, learning, and thought pattern is affected) (Maric et al. 2004). A biological disposition, including alterations in the genetic makeup, the neurotransmitter system, the immune system, and several other psychological issues, contributes to the development of ScZ. Prenatal risk factors and childbirth complications may also lead to the development of the disorder. Apart from these early risk factors, several traumatic and drug abuse situations during infancy and adolescence (a sensitive period in brain development), such as cannabis misuse (surfacing in adolescents), may influence the onset of symptoms, progression, and risk of disease relapse. When the timing and sum of the individual risk factors interact, they can disrupt neural regeneration and contribute to ScZ. However, the complete interplay of this multifactorial process is still unknown (Löhrs and Hasan 2019). This book chapter has discussed the potential role and mechanism of different, well-known antipsychotic drugs in treating ScZ, which are considered the initial stage of ScZ treatment. Antipsychotic drugs are generally divided into two major classes: first-generation antipsychotics (FGA) and second-generation antipsychotics (SGA). FGAs are generally dopamine antagonists and act on the neurotransmitter pathways, while SGAs have an affinity toward both dopamine and 5HT2 receptors that bind to another neurotransmitter receptor-like serotonin (Ijaz et al. 2020). Moreover, some of the emerging strategies like omega-3 fatty acids, melatonin administration, and cannabidiol have been shown to reverse the symptoms associated with ScZ, which have also been discussed in this chapter.

10.2 First-Generation Antipsychotics (FGAs)

The use of FGAs has declined with the discovery of SGAs. However, FGAs still find a way onto the prescription list of antipsychotics due to their low costs (Elbe 2010).

Being the dopamine receptor D2 (D2R) antagonists, the FGAs inhibit the neurotransmission of dopaminergic neurons in four different dopamine pathways, which are mesocortical, mesolimbic, nigrostriatal, and tuberoinfundibular (Gründer et al. 2009; Sarkhel 2009). Studies suggest that dysfunction of mesocortical and mesolimbic pathways is associated with impairments and disturbances in cognition and emotions and induces negative symptoms. High doses of typical antipsychotics can block this pathway, causing secondary negative symptoms and cognitive effects, secondary negative symptoms, and mental outcomes (Gründer et al. 2009; Sarkhel 2009). The overactivity of the mesolimbic pathway affects the pathophysiology of positive symptoms of ScZ. The effectiveness of the FGAs is best when they block about 72% of the D2 dopamine receptors in the brain (Barbui et al. 2016). In the nigrostriatal pathway, the antagonism of D2Rs leads to an increased risk of extrapyramidal symptoms. The most common typical antipsychotics associated with

extrapyramidal symptoms are haloperidol and fluphenazine (Divac et al. 2014; Li et al. 2016). Dopamine acts as a prolactin-inhibiting factor, as dopamine released from the tuberal region of the hypothalamus binds to D2Rs and inhibits the prolactin secretion from the anterior pituitary gland lactotrophs. So, when the typical antipsychotic blocks the D2Rs in the tuberoinfundibular pathway, it increases prolactin levels in the blood, known as hyperprolactinemia (Torre and Falorni 2007).

10.2.1 Examples of the First-Generation Antipsychotics

Phenothiazines, a group of heterocyclic compounds containing nitrogen and sulfur, and after being discovered in 1883, its derivatives were first administered commercially as antipsychotic therapy in the USA around the 1950s (Mann and Marwaha 2022; Pluta et al. 2011). Phenothiazines are generally prescribed along with atypical antipsychotics like clozapine. Phenothiazines are also administered in combination with non-pharmacological psychotherapeutic therapy, like narrative, meta-cognitive, and mindfulness therapy, for optimal results (Patel et al. 2014). Phenothiazines are further divided into three subtypes based on the diversity of side chains attached to the same three-ringed structure, resulting in a difference in potency among the phenothiazines (Jaszczyszyn et al. 2012). Commonly known, three subtypes of phenothiazines, such as aliphatic, piperidine, and piperazine, are used to manage the psychotics.

Aliphatic phenothiazines such as chlorpromazine are marketed as thorazine and largactil. These antipsychotics exhibit strong D2R, 5HT2, muscarinic, alpha 1 adrenergic, and antihistamine activity and act as strong antagonists of D2R and other similar receptors like D3R and D5R. Chlorpromazine and other low-potency antipsychotics lead to a high number of anticholinergic side effects and reduced rates of extrapyramidal side effects (Brunton et al. 2010). Chlorpromazine, among the typical antipsychotic, has this uncommon ability to affect serotonin receptors more than D2Rs, making it an atypical antipsychotic equivalent rather than typical antipsychotics. It also binds to the D1R with high affinity unlike other drugs of this category (McKim 2007). It is a significant first-generation antipsychotic as it is used for comparison with other typical antipsychotics to measure equivalence potency (Rijcken et al. 2003). Few other low-to-medium-potency antipsychotics having aliphatic side chains is levomepromazine, promazine, triflupromazine, etc. (Wisher 2012).

Piperidine phenothiazines, which have piperidine side chains, are low-to-medium-potency antipsychotics. Mesoridazine, one of the piperidine, exhibits strong D2 dopamine and 5HT2 activity; in this antipsychotic, alpha-1 adrenergic and antihistamine activities are higher than muscarinic activity (Salimi et al. 2009). Another piperidine phenothiazine, thioridazine, contains a very high affinity toward most receptors like D2 dopamine, 5HT2, muscarinic, alpha-1 adrenergic, and histamine H1 receptors (Salimi et al. 2009). Thioridazine does have quite relatively sedating and anticholinergic effects, as well as the hypotensive effects, which are

also high, while the extrapyramidal side effects are low. The branded version of this drug was withdrawn from the market post-cardiac adverse events. However, the US market still manufactures generic versions, but it is rarely administered. Some other examples of commonly used antipsychotics of piperidine phenothiazines are pericyazine and pipotiazine (Zhang et al. 2013).

Piperazine phenothiazine antipsychotics having piperazine side chains are medium-to-high-potency antipsychotics. One of the piperazine phenothiazine antipsychotic perphenazine, also marketed as Trilafon, has a very strong affinity toward the D2R and the 5HT2 receptor. On another hand, muscarinic activity is relatively low while alpha-1 adrenergic and antihistamine are moderate and high, respectively (Salimi et al. 2009). Perphenazine has low sedating, anticholinergic, and hypotensive effects, while extrapyramidal side effects are high (Hartung et al. 2015; Zhang et al. 2013) Another piperazine, fluphenazine (Prolixin), has a very high D2R affinity, but affinity toward antihistamine and 5HT2 activity is moderate while muscarinic activity and alpha-1 adrenergic activity are deficient (Matar et al. 2018). In the case of fluphenazine, sedating, anticholinergic, and hypotensive effects are very low, while extrapyramidal side effects are very high (Kong and Yeo 1989). Trifluoperazine, another antipsychotic belonging to the piperazine class, has a very high affinity toward D2 dopamine and 5HT2 activity, but the muscarinic activity exhibited is low. In contrast, the alpha-1 adrenergic and antihistamine activities are moderate. Trifluoperazine has low sedating, anticholinergic, and hypotensive effects while extrapyramidal side effects are very high (Kahn and Sommer 2015).

There are a few antipsychotics, such as butyrophenones, thioxanthenes, dibenzepines, and diphenylbutylpiperidines, which belong to the category of non-phenothiazine antipsychotics. Butyrophenones are known as high-potency first-generation antipsychotics. The few widely used drugs from this chemical class are benperidol, droperidol, and haloperidol (Froemming et al. 1989). Haloperidol, marketed as Haldol, has a very high affinity toward the D2 receptor while moderate in the case of the 5HT2 receptor. It is the most commonly administered drug in class. The haloperidol has very low muscarinic, alpha-1 adrenergic, and antihistamine activity. The haloperidol's sedating, anticholinergic, and hypotensive effects are extremely low, while extrapyramidal side effects are very high (Froemming et al. 1989).

Thioxanthenes non-phenothiazine are known as low-to-medium-potency first-generation antipsychotics. Fluphenazine (Prolixin) is one of the thioxanthenes and has a very high D2R activity. It has moderate 5HT2 and antihistamine activity, while the muscarinic and alpha-1 adrenergic activity is very low. The adverse effects like the sedating, anticholinergic, and hypotensive effects of fluphenazine are low, while extrapyramidal side effects are very high. Other commonly used drugs of this genre are clopenthixol, thiothixene, zuclopenthixol, etc.

Dibenzepines are low to medium-potency typical antipsychotics. Commonly used dibenzepines like loxapine, also known as loxitane, have a high affinity toward the D2 dopamine, the 5HT2, and the antihistamine receptor. In this drug, the muscarinic activity is moderate, while alpha-1 adrenergic receptivity is high. The sedating, hypotensive, and extrapyramidal side effects of lozapine are moderate,

while the anticholinergic effects are quite low. Clotiapine is another example of the class dibenzepines antipsychotic (Hartung et al. 2015; Zhang et al. 2013).

Pimozide, which belongs to diphenylbutylpiperidines, is a high-potency antipsychotic marketed under the brand name Orap. Pimozide has a high affinity for the D2 dopamine receptor, and it is administered orally. It has low adverse effects like sedating and anticholinergic effects. The extrapyramidal side effects of this drug are very high, while the hypotensive effects are very low (Hartung et al. 2015; Zhang et al. 2013). Fluspirilene is another example; diphenylbutylpiperidines, a typical antipsychotic drug marketed under the names Redeptin and Imap, which is administered intramuscularly (Janssen et al. 1970; van Epen 1970).

10.3 Second-Generation Antipsychotics

A vast range of second-generation antipsychotic drugs is available in the market. They usually include the atypical antipsychotic drugs since they are new to the system and have higher expectations than the previous ones, like FGAs. Second-generation or atypical antipsychotics showed higher affinity toward serotonin 5-HT2A receptors than toward the D2 receptors. Some of the second-generation antipsychotics are as follows:

10.3.1 Clozapine

Clozapine is an atypical antipsychotic drug with no extrapyramidal side effects (EPS) (Shen 1994). It has been approved by the FDA in the 1990s (Hippius 1989; Kane et al. 1988). It helps in minimizing the risk of suicidal thoughts in schizophrenic patients (Meltzer et al. 2003). Clozapine shows a lower affinity for D2Rs and relatively greater affinity for serotonin (5-hydroxytryptamine) and 5-HT2A receptors specifically, but also for noradrenergic receptors (α1 and α2), muscarinic acetylcholine receptors, histamine, and other dopamine (DA) subtype receptors. Schizophrenic patients with continuous violent behavior have shown consistent clinical benefits (Buckley 1997; Volavka et al. 2004). Clozapine is also suggested as an efficient drug in psychotic refractory depression (Dassa et al. 1993). The mechanism of clozapine is not clear but may be the result of immune response to direct toxicity (Gerson and Meltzer 1992). There is also emerging evidence that clozapine may be associated with acute interstitial nephritis (Au et al. 2004), pancreatic (Koller et al. 2003), and fatal thromboembolism (Knudson et al. 2000).

10.3.2 Olanzapine

Olanzapine is a high-efficacy antipsychotic drug with a structural analog of clozapine and a similar pharmacologic profile. To other atypical antipsychotics, olanzapine is considered superior (Citrome et al. 2019; Komossa et al. 2010); D1–D5 dopamine receptors, 5-HT2A, 5-HT2C, 5-HT6 serotonin receptors, M1 muscarinic, H1 histamine, and adrenergic receptors have a clinically relevant affinity (Bymaster et al. 1996). Olanzapine causes transient prolactin elevations and few extrapyramidal side effects (Tollefson et al. 1997). A major difference between the two drugs (olanzapine and clozapine) is the high affinity of olanzapine for the receptors of D2 dopamine and its high-dosage potency. It contains a lower binding affinity for D2 and 5-HT2A receptors than risperidone and paliperidone (Johnson et al. 2011; Schotte et al. 1996); like other atypical antipsychotic drugs, olanzapine is also associated with severe gain of weight (Casey and Zorn 2001), hyperglycemia (Lindenmayer et al. 2002), diabetes (Sernyak et al. 2002), and hyperlipidemia (Melkersson et al. 2000; Rice et al. 1992).

10.3.3 Risperidone

Risperidone is a second-generation (atypical) antipsychotic medication used for positive symptoms of ScZ worldwide. Antipsychotics like risperidone and active metabolites of risperidone, paliperidone (9-hydroxyrisperidone), are associated molecules used to treat ScZ and other related disorders to it. Both drugs contain a high affinity for D2 and 5-HT2A receptors and are atypical antipsychotics. Risperidone and paliperidone have worked differently in terms of different activities like mitochondrial function, neuroreceptor binding, and movement with repercussions for neuronal firing (Seeger et al. 1995).

10.3.4 Paliperidone

Paliperidone acts as the active metabolite of risperidone and has been approved for the short-and long-term treatment of ScZ in adults and adolescents. Paliperidone monotherapy and adjunctive therapy are considered acute treatment of schizoaffective disorder that worked as mood stabilizers and/or antidepressants. Risperidone is metabolizing to paliperidone and both drugs show similar and effective binding properties and clinical effect profiles. Paliperidone diffuses slower through biological membranes because it is less lipophilic than risperidone. However, the passive permeability is quite similar in both paliperidone and risperidone (Feng et al. 2008). A double-blind experiment was performed in 2011 (Pandina et al. 2011), where paliperidone was shown non-inferior to risperidone. In addition, the

tolerability and safety of paliperidone palmitate are built similar to that of RIS-LAI. Risperidone shows no affinity for cholinergic receptors (Janssen-Cilag 2005).

10.3.5 Ziprasidone

The US Food and Drug Administration (FDA) authorized ziprasidone hydrochloride, an oral formulation, in February 2001 as a clinically effective agent in the treatment of patients with ScZ promoting it as a more acceptable alternative to other recent antipsychotic treatments. Ziprasidone has a favorable tolerability profile, with notable benefits such as low weight gain, an increase in LDL or total carbohydrates such as cholesterol and triglycerides, or glycemic control compromise. When patients shift from previous medicines to ziprasidone, they may see a moderate improvement in these measures (Greenberg and Citrome 2007). Ziprasidone is also non-anticholinergic, rarely causes a prolonged or clinically significant increase in prolactin levels or postural hypotension, and has few extrapyramidal adverse effects. Ziprasidone is administered as a twice-daily oral medication to be taken with food or else its bioavailability subsides when not taken in combination with food (Hamelin et al. 1998). The FDA approved the short-acting intramuscular ziprasidone mesylate formulation as a therapeutic medication for acute agitation in individuals with ScZ in June 2002 (Goodnick 2001). Ziprasidone was expected to outperform control in the treatment of the different symptom criteria of ScZ such as depressive, cognitive, and/or negative symptoms. Its clinical efficacy appears to be comparable to quetiapine, but slightly lower than olanzapine or risperidone (Greenberg and Citrome 2007).

10.3.6 Quetiapine

Quetiapine, a dibenzothiazepine derivative, is one of several new "atypical" drugs that has been reported to have played a significant role as a therapeutic medication for the treatment of the core symptom criteria of ScZ (Purdon et al. 2001; Velligan et al. 2002). Quetiapine has more in vitro binding affinity for serotonin 5-HT2 receptors as compared to dopamine D2 receptors and might be slightly less effective in lowering symptoms than risperidone and olanzapine but might also cause less weight gain, and fewer adverse effects (Asmal et al. 2013).

10.3.7 Aripiprazole

Aripiprazole is a second-generation antipsychotic and is considered to be the first antipsychotic to have agonist characteristics at the dopamine D2 autoreceptors. On

November 15, 2002, the FDA authorized aripiprazole for ScZ as an oral tablet formulation with a dosing range of 2–30 mg. Some of the available therapeutics are orally disintegrating tablets, oral solution, and an aqueous intramuscular injection solution. In some patients, aripiprazole can help with three symptom criteria of ScZ. It has a lower EPS liability than FGAs (e.g., haloperidol) (Leucht et al. 2013), lower weight gain, and metabolic liabilities than SGAs (e.g., clozapine) and plays no role in developing hyperprolactinemia (Kane et al. 2002). The long-acting injectable forms of aripiprazole are aripiprazole monohydrate (AM) and aripiprazole lauroxil (AL).

10.4 Other Drugs for Treatment and Management of ScZ

Novel antipsychotic medications have become the mainstay in treating schizophrenic patients with better efficacy and satisfying tolerability. Besides other antipsychotics, novel antipsychotics have a more favorable side effect profile of low prolactin levels to avoid hyperprolactinemia and insignificant extrapyramidal side effects (Maric et al. 2016). Brexpiprazole, cariprazine, lurasidone, blonanserin, lumateperone, etc., are some newer drug formulations in the list of antipsychotics.

10.4.1 Brexpiprazole

The U.S. FDA approved brexpiprazole as a new antipsychotic drug for ScZ and related depressive disorder in July 2015. Brexpiprazole is also used as adjunctive therapy to antidepressants in adults (Markovic et al. 2017). Sedation and weight gain due to low H1 receptor antihistamine activity are lower in brexpiprazole than in aripiprazole (Stahl 2016a). Being an activity modulator of serotonin-dopamine and showing better clinical efficacy and acceptability, it has been proven to be an effective alternative to typical and atypical antipsychotics. Brexpiprazole is a partial agonist at serotonin 1A (5-HT1A) receptors and the dopamine D2 receptors, a potent antagonist at 5-HT2A, α1B, and α2C adrenergic receptors (Maeda et al. 2014). It also demonstrates structural similarity with aripiprazole. However, aripiprazole has higher intrinsic agonist activity at the D2 receptor than brexpiprazole (Stahl 2016a). Brexpiprazole, once daily taken drugs, can be consumed with or without food; having doses range 0.25, 0.5, 1, 2, 3, and 4 mg tablets are marketed (Garnock-Jones 2016).

10.4.2 Cariprazine

Cariprazine, a novel antipsychotic drug, is efficient in treating the negative and extrapyramidal symptoms in schizophrenic patients (Garnock-Jones 2017). In 2015,

the United States FDA approved cariprazine in a dosage range of 1.5, 3, 4.5, and 6 mg capsules to consume one capsule per day. Doses above 6 mg are responsible for enhancing the risk of adverse reactions without adding any benefits (Garnock-Jones 2017), and cariprazine has high D3 antagonist properties. For D2R partial agonism, brexpiprazole has the strongest affinity and shows an antidepressant effect, followed by aripiprazole and cariprazine (Stahl 2016a). In the case of cariprazine, along with other antipsychotics, an increased mortality rate in elderly patients comes with a black box warning. Cerebrovascular incidents, such as stroke and neuroleptic malignant syndrome, tardive dyskinesia, metabolic changes, and orthostatic hypotension, are some of the rare effects of cariprazine (Mucci et al. 2021). For minimizing agitation and akathisia comparable to other antipsychotics, cariprazine is considered a suitable agent as it also relieves certain symptoms of ScZ (Stahl 2016b).

10.4.3 Lumateperone

Lumateperone is a new FDA-approved antipsychotic that possesses a unique pharmacologic effect for the treatment of adult schizophrenic patients authorized in December 2019. The mechanistic action of lumateperone involves a presynaptic partial agonism and postsynaptic antagonism at dopamine D2 receptors (Davis and Correll 2016; Krogmann et al. 2019; Vyas et al. 2020), causing less dopamine release as well as postsynaptic dopamine blockage, responsible for significant depletion of dopaminergic signaling in comparison with other antipsychotic medication (Snyder et al. 2015), which leads to sedation, cognitive, and other metabolic side effects. Lumateperone is also an antagonist of the 5-HT2A receptor. It induces sleep and brings down aggression at a lower dose but has antipsychotic and antidepressant effects at higher doses (Snyder et al. 2015).

10.5 Polypharmacy

The term polypharmacy was originally coined to refer to the problems of multiple drug consumption during the treatment of a disease (Friend 1959). It is defined as the concomitant prescription of two or more antipsychotic medications. Achieving the therapeutic goals for the proper treatment of ScZ remains a challenge, despite the availability of numerous antipsychotics (Ballon and Stroup 2013). Antipsychotic monotherapy (APM), instead of antipsychotic polypharmacy (APP), is considered the gold standard for the treatment of ScZ. However, according to an observation based on randomized controlled clinical trials, about 20–40% of the patients show no response to APM (Pae 2020). Studies suggest that a subset of patients with ScZ require a differentiated therapeutic approach beyond traditional therapeutic strategies such as monotherapy of antipsychotics.

10.5.1 Reasons for Antipsychotic Polypharmacy

With insufficient efficacy and inadequate response to the positive symptoms of antipsychotic monotherapies, clinicians find reasons to rely on APP in the management of positive and negative symptoms, especially positive symptoms (Pae 2020). A survey on 66 patients with ScZ receiving antipsychotic polypharmacy treatment examined the reason for its use at two veterans administration medical centers in the USA (Correll et al. 2011; Ito et al. 2005) and found positive and negative symptoms were reduced by 61% and 20%, respectively (Ballon and Stroup 2013).

Clozapine is considered the antipsychotic drug of choice for treatment-resistant ScZ (McEvoy et al. 2006). To overcome the resistance or tolerance to the effects of one drug, clinicians overleap one drug while titrating the other, or else lack of tolerance or side effects will not be able to help us achieve an effective dose of one antipsychotic (Barnes and Schizophrenia Consensus Group of British Association for Psychopharmacology 2011). In the case of polypharmacy, to treat ScZ, clinicians use various combinations of medications such as mood stabilizers, antidepressants, anxiolytics, or hypnotics, along with single or multiple antipsychotics (Lin 2020). There are several clinical shreds of evidence that encourage patients to take concomitant antipsychotics. Clinicians may use APP to target and treat comorbidities as well as underlying illnesses such as cognitive dysfunction, anxiety, insomnia, sustained aggression, impulsive behavior, lack of initial improvement from primary AP, avoidance of high-dose AP therapy, etc. (Barnes and Paton 2011; Lähteenvuo and Tiihonen 2021; Lehman et al. 2004). For example, sometimes clinicians may prescribe additional sedative antipsychotics for sleep disorders instead of benzodiazepines to achieve better results (Baandrup 2020).

Another role of APP is to increase the efficacy of antipsychotic medications in treating schizophrenic patients with mood symptoms or behavioral changes (Palmer et al. 2018). There are several other diversities in APP such as cross-titrations, faster treatment response, patients with severe and longer duration of illness and complexity, shorter hospital stays, avoidance of high dose of APM (Hjorth 2021), synergistic effect in treatment using different pharmacological antipsychotics (Maric et al. 2004), and combinations of different formulations of APs. It also helps in attenuation of adverse effects like weight gain and metabolic issues (Hjorth 2021).

One of the main goals of APP as a pharmacological rationale for achieving broader clinical effect and greater therapeutic potential is receptor binding (Jacob et al. 2013). This can be achieved by directly focusing on optimizing dopamine D2 receptor occupancy or approaching a range of non-dopamine receptors such as serotonergic, glutamatergic, and adrenergic. The occupancy of these receptors may be associated with an overall favorable response to treatment and the etiology of positive and negative symptoms (Barnes et al. 2009a, b; Freudenreich and Goff 2002; Kreyenbuhl et al. 2007a; Seeman 2006; Zink et al. 2010). Clinicians may add more than one antipsychotic medication in the transition from one antipsychotic to another when there is cross-tapering of the doses of both drugs (Grech and Taylor 2012) to manage the risk of disease instability. In addition, Prescribing Observatory

for Mental Health (POMH-UK) in the United Kingdom conducted national audits which found that the most common reason to prescribe combined antipsychotic medications was a period of crossover while switching from one antipsychotic to another (Procyshyn et al. 2010) to increase efficacy when the response to antipsychotic monotherapy was disappointing (Kreyenbuhl et al. 2007b).

10.5.2 Risk Associated with Antipsychotic Polypharmacy

The evidence regarding the possible harms of antipsychotic medications or APP seems more substantial. It has been reported that APP is associated with several disadvantages, which discourage its use in the treatment of ScZ. The most effective antipsychotics, olanzapine and clozapine, are associated with a risk of metabolic side effects (Komiya et al. 2018). The main adverse association was observed with excessive antipsychotic dosages in patients with other psychiatric comorbidities (Sakurai et al. 2013), which leads to further complexity. A high dosage of medications provokes adverse effects with the increased risk of drug–drug interactions and reduced adherence (Dome et al. 2007; Hashimoto et al. 2012). Problems associated with high dose also include extrapyramidal symptoms, cognitive impairment (Constantine et al. 2015), sexual dysfunction (Constantine et al. 2015), paralytic ileus (Correll et al. 2007), diabetes (Mitchell et al. 2013), QTc prolongation (Barbui et al. 2016), and cognitive dysfunction (Pae 2020).

10.6 Emergence of Serotonergic Agents for ScZ Treatment

There are several drugs that target the serotonin receptors (5-HTR), and these have been intensively explored and are being developed for patients with ScZ (Meltzer and Massey 2011). The seven selective 5-HTR compounds undergoing the clinical trials in ScZ are as follows: pimavanserin (selective 5-HT2AR inverse agonist) (Meltzer et al. 2012), vabicaserin (selective 5-HT2CR agonist) (Dunlop et al. 2011), ondansetron (Akhondzadeh et al. 2009), tropisetron (Noroozian et al. 2013) and granisetron (Khodaie-Ardakani et al. 2013) (selective 5-HT3R antagonists), idalopirdine (Arnt et al. 2010), and AVN-211 (Morozova et al. 2014) (selective 5-HT6R antagonists) (Morozova et al. 2014).

10.6.1 Pimavanserin

The elevation in the activity of dopaminergic neurotransmission in the nucleus accumbens contributes to the positive symptoms associated with ScZ (Meltzer and Huang 2008). On dopaminergic neurons, 5-HT2AR is present, which are usually

excitatory and regulate dopaminergic neurotransmission (Khilnani and Khilnani 2011). The pimavanserin (ACP-103), a selective 5-HT2AR inverse agonist, can stabilize and reduce the activity of 5-HT2AR (Abbas and Roth 2008). This therapeutic activity ensures a significant control of serotonin neurotransmission, with decreased undesirable side effects. Pimavanserin is currently under active study and development as a therapeutic agent for ScZ (Cummings et al. 2014) and psychosis associated with Parkinson's disease (Friedman 2013) and Alzheimer's disease (Meltzer et al. 2012). A randomized clinical trial (RCT) was conducted for 6 weeks by Meltzer et al. on 423 patients having chronic ScZ who were given a low dose of a combination of either risperidone (2 mg/day) and pimavanserin or a low dose of haloperidol (2 mg/day) and pimavanserin and this condition was compared with patients who were treated with a high amount of risperidone (6 mg/day + placebo) or just haloperidol (2 mg/day + placebo). The antipsychotic effect was shown to be more in pimavanserin and a low dose of risperidone as compared to a high dose of risperidone. Similarly, a low dose of pimavanserin and a low dose of haloperidol decreased the extrapyramidal side effects in contrast to haloperidol + placebo (Cummings et al. 2014). Pimavanserin has also been found to be effective in treating patients with Parkinson's disease psychosis (PDP) (Liu et al. 2014).

10.6.2 Vabicaserin

Vabicaserin (SCA-136) is a novel anorectic and shows antipsychotic-like efficacy with no weight gain and extrapyramidal symptoms in preclinical trials of 5-HT2C agonists (Garay et al. 2016). Thus, selective 5-HT2CR agonists are a potential antipsychotic medication with more tolerability and safety. In phase II of RCT (NCT00563706), the tolerability, safety, and efficacy of vabicaserin in adult patients with chronic ScZ were evaluated. The PANSS (Positive and Negative Symptom Scale) total score on Day 28 showed a change from baseline that was not significantly different from the placebo (Shen et al. 2014). However, Shen et al. reported positive outcomes in patients with chronic ScZ while treating them with vabicaserin. A total of 314 subjects were randomized into four groups for treatment: olanzapine 15 mg/day or placebo, vabicaserin 200 or 400 mg/day. On the PANSS negative subscale, both the vabicaserin groups showed significant improvement over the placebo in terms of change from baseline. Vabicaserin was quite well-tolerated, and there were no severe side effects. Weight gain was induced by olanzapine but not by vabicaserin (Thompson and Lummis 2006).

10.6.3 Ondansetron, Tropisetron, and Granisetron

5-HT3 receptors are located in the central and peripheral nervous systems (Funahashi et al. 2004). These receptors are majorly present in the areas of the

brain involved in depression, anxiety, cognition, vomiting reflex, and emotions (Barnes et al. 2009a, b).

Antagonists of 5-HT3R treat vomiting and nausea after cancer chemotherapy, surgery, or radiation therapy (Kondo et al. 2018). It has also been shown by Kondo et al. that agonists of 5-HT3 receptors are capable of inducing antidepressant effects and can stimulate hippocampal neurogenesis (Zhang et al. 2006). The drugs like ondansetron, tropisetron, and granisetron are the antagonists of the 5-HT3 receptor that demonstrated improvement in the negative symptoms associated with ScZ. The improvement in both cognitive impairment and negative symptoms was seen in chronic ScZ patients when treated with ondansetron in RCTs. When compared to placebo with haloperidol, ondansetron combination with haloperidol provided a significantly larger improvement on the PANSS overall scale and subscales for negative symptoms, general psychopathology, and cognition at the endpoint. Therefore, for chronic and treatment-resistant ScZ, ondansetron is a potential adjunctive drug for improving the performance and lowering some harmful side effects of antipsychotic therapy, notably for negative and cognitive symptoms (Shiina et al. 2010).

10.6.4 Tropisetron

A dose of tropisetron in patients with ScZ showed improved cognitive abilities. Shiina et al. performed the first randomized, double-blind, placebo-controlled trial to show that adjunctive tropisetron is safe and effective for treating cognitive impairments in ScZ. As a result, not only the improvement in cognition was seen, but improved auditory sensory gating P50 inhibition deficits in ScZ patients were also seen (Shiina et al. 2010). Tropisetron is also a partial agonist of α7 nicotinic acetylcholine receptor (nAChR). An agonist of α7 nAChR receptor has been demonstrated to reduce the cognitive deficits and impaired sensory gating represented by P50 inhibition deficits. Therefore, 1 day of tropisetron treatment alleviated both cognitive and P50 inhibition impairments, implying that longer-term intervention with α7 nAChR agonists for both deficits in ScZ could be beneficial (Xia et al. 2020). Ardakani et al., in their study, found improvement in patients with stable ScZ when treated with granisetron (Khodaie-Ardakani et al. 2013).

10.6.5 Selective 5-HT6R Antagonists

In brain areas in rats like the hippocampus, striatum, memory-related areas, nucleus accumbens, olfactory tubercle, and limbic areas, the 5-HT6R is exclusively expressed (Monsma et al. 1993). 5-HT6Rs are mainly located on GABAergic neurons. Polymorphisms in the 5-HT6 receptor have been linked to cognition-related disorders like ScZ and dementia. Modification of 5-HT6 receptor activity

affects the transmission of various memory-related neurotransmitters (Mitchell et al. 2013). Idalopirdine and AVN-211 (Avineuron) are 5-HT6 antagonists that demonstrated precognitive effects in an animal model (Mitchell et al. 2013). AVN-211 (CD-008-0173) enhances antipsychotic and some procognitive effects of antipsychotic medication, according to a pilot RCT in a small number of stable patients ($N = 47$) (Galimberti and Scarpini 2015; Morozova et al. 2014).

10.7 Emerging Strategies to Treat ScZ

10.7.1 Melatonin

Research studies have shown positive outcomes of adjunctive melatonin therapy in the case of sleep, metabolic profile, and tardive dyskinesia in patients with ScZ. The studies have also proven the therapeutic benefits of the antioxidant and neuroprotective effects of melatonin in the adjunctive treatment that attenuates the side effects associated with second-generation antipsychotics (Duan et al. 2021). Apart from enhancing circadian rhythms, and metabolic outcomes, it has no significant benefit in improving cognitive function in individuals with ScZ (Duan et al. 2021). Sleep and circadian dysfunction are the most common features which are noticed in patients with ScZ. Based on the study, researchers can conclude that decreased secretion of melatonin is commonly found in ScZ patients, and benzodiazepines are largely used to treat sleep disruption in ScZ. Melatonin (*N*-acetyl-5-methoxytryptamine) is a hormone that is secreted naturally by the pineal glands at night (Morera-Fumero and Abreu-Gonzalez 2013). Melatonin shows neuroprotective and antioxidant effects and is often effective in reducing weight, as shown in Fig. 10.1, which is usually increased with the first antipsychotic intake during ScZ treatment. Melatonin has two receptors, i.e., MT1 and MT2, which are G protein-coupled receptors (Stauch et al. 2020). Melatonin also reduces benzodiazepine intake as few ScZ patients are given benzodiazepines and they show withdrawal symptoms due to the development of drug dependence (Morera-Fumero and Abreu-Gonzalez 2013) In 2014, Modabbernia et al. reported that in the first episode of ScZ, melatonin could cause weight gain, abdominal obesity, and the different conditions related to carbohydrate or lipid dysregulation such as hypercholesterolemia, hyperlipidemia, hyperglycemia, and hypertension. Melatonin has been used since 1920, and according to researchers, melatonin levels have been used to distinguish the types of ScZ. In paranoid ScZ, the melatonin level is quite lower than in other subtypes of ScZ (Modabbernia et al. 2014).

10.7.2 Cannabidiol

Current antipsychotic treatment available for ScZ has reported multiple adverse effects. According to the latest research, cannabidiol (CBD) can be used as a

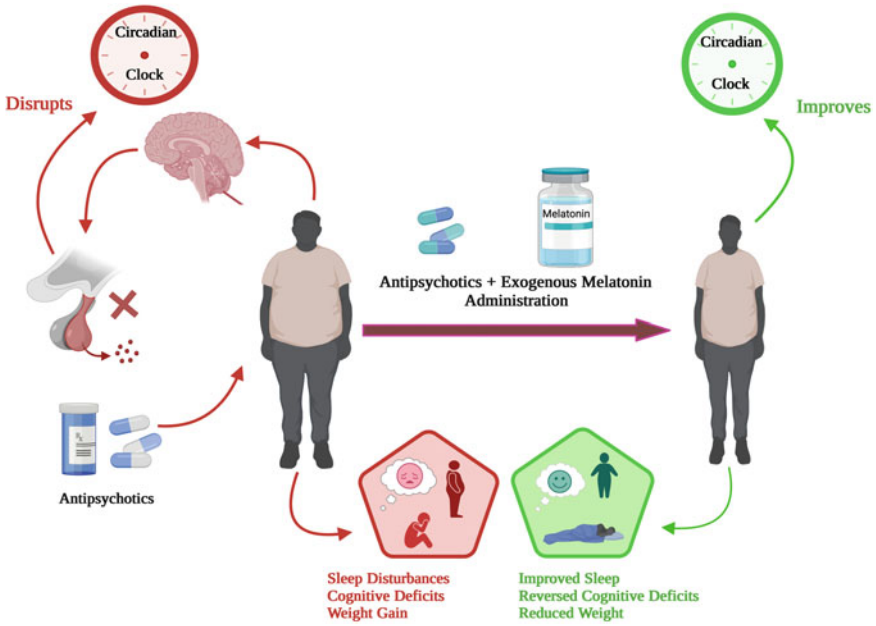

Fig. 10.1 Disruption of Circadian Rhythms Are Observed in the ScZ Patients. This happens due to dysfunction in the pineal gland to produce melatonin. It is seen that when the patients are administered with exogenous melatonin along with antipsychotics, it results in improved cognitive function and loss of weight

treatment opportunity for ScZ. CBD was first identified by Roger Adams in the 1940s and was extracted from the cannabis sattva plant. CBD primarily targets the brain's endocannabinoid system. It appears to have antipsychotic properties, as evidenced by preclinical and clinical research, and also helps in reducing the positive, negative, and cognitive symptoms of ScZ (Schoevers et al. 2020). According to a study, schizophrenic patients, based on DSM, were taken in which CBD administration showed a positive effect on cognition, but no adverse effect was reported (Stahl 2016a). The main psychoactive ingredient in cannabis is delta-9-tetrahydrocannabinol (THC), which has anxiogenic, psychotomimetic, and asymmetric effects. CBD has anxiolytic, antipsychotic, and anticonvulsant properties with no effect on memory. CBD has reduced hyperlocomotion involved in amphetamine and ketamine. CBD prevents the development of prepulse inhibition deficits in hypertensive rat strains (García-Gutiérrez et al. 2020). Even CBD has been reported to reverse the methoxy methanol induced alteration and ScZ-like symptoms, which are not reduced by haloperidol. However, more studies are required to know the exact dosage and molecular mechanism of action of CBD to manage symptoms of ScZ (Davies and Bhattacharyya 2019).

10.7.3 Omega-3 Fatty Acids

Omega-3 fatty acids are a vital form of fatty acids that are not produced by the human body and are required for survival. Our regular meals provide us with enough fatty acids essential for bodily functions. The omega-3 polyunsaturated fatty acids (PUFA), found in both the marine and terrestrial animal food products, have gained humongous significance recently. They play a significant role in various biological functions of the body, including cell signaling, blood clotting, skeletal muscle metabolism, etc. (Gammone et al. 2018), and especially show anti-inflammatory and antioxidant activity, further improving both mental and physical health. The intake of these omega-3 fatty acids in the diet may have a favorable effect on cognitive performance as well. Omega-3 fatty acid supplementation may improve cognitive functioning in ScZ and affective disorders, according to existing evidence derived primarily from mechanistic models and animal trials (Knöchel et al. 2015). The omega-3 polyunsaturated fatty acids have been reported as a positive factor in improving the psychopathology in ScZ, largely involving positive symptoms (Goh et al. 2021). A recent study performed by Goh et al. showed positive effects of these fatty acids on serum triglycerides. ScZ usually involves abnormalities in phospholipid metabolism, and it is known that the membranes in the neural system include phospholipids that are rich in unsaturated fatty acids. Therefore, it has been reported that essential omega-3 polyunsaturated fatty acids can play a significant role in the treatment of ScZ (Emsley et al. 2003).

10.7.4 Vitamins for the Management of ScZ

Vitamins play a vital role in cellular metabolism, and a low level of vitamin B is commonly seen in ScZ patients, as vitamin D deficiency is also reported in ScZ (Bansal and Chatterjee 2022). It has been reported that vitamin D deficiency can increase the risk of ScZ (Brown and Roffman 2014). In one study, vitamin D showed that offspring of migrants with dark skin when migrating to cold climates have a greater risk of ScZ due to low vitamin D levels during gestation. So, this study proves that vitamin D level is related to the onset of ScZ (Cui et al. 2021). Vitamins C and E have antioxidant properties, and it is hypothesized that vitamin E acts as a pro-antioxidant. Vitamin C has shown a positive effect on 10 out of 12 ScZ patients when given a dose of 8 g/day maximum. It also reduces the deleterious effect of vitamin E on ScZ patients and shows an effect on neuronal differentiation and migration. During a study, it was seen that during the second trimester of pregnancy, low vitamin A levels could increase the odds of developing Z (Brown and Roffman 2014).

10.7.5 Curcumin

Curcumin is extracted from Curcuma longa, which has antioxidant and anti-inflammatory properties. When curcumin is used in combination with piperine, it reduces psychotic symptoms. In a 2019 study by Chiu et al., 15 patients were given curcumin with a combination of piperine for 16 weeks at 1 and 4 g/day as pre- and post-treatment in two groups. It showed show positive effects and enhancement of cognitive symptoms with no adverse effects in both groups (Wynn et al. 2018). Curcumin-loaded nanophytosome (CNP) shows a positive impact on ketamine-induced rats, and it not only improves curcumin bioavailability but can also show better neuroprotective effects on ketamine-induced neuronal deficits and oxidative damage. Therefore, CNP can be a promising drug delivery system (Moghaddam et al). In 2017, the first double-blind placebo-controlled study was done for curcumin based on brain-derived neurotrophic factors (BDNF). In this study, 36 patients with ScZ were given curcumin for 8 weeks at 360 mg/day, and BDNF levels subsequently increased. This study did not show a positive effect on cognition or other clinical symptoms, whereas in another study conducted for 8 weeks where ScZ patients were given 300 mg of curcumin, cognition was improved, and interleukin 6 (IL-6) levels were reduced (Moghaddam et al. 2021).

10.7.6 Spinacia Oleracea

Spinacia oleracea (spinach) consists of multiple medicinal properties. Its seeds consist of antioxidant, neuroprotective, anti-inflammatory, neuroprotective, anti-epileptic properties, and anti-Alzheimer's properties. Spinach has even shown antistress and antidepressive properties by reducing blood corticosterone and increasing glutamate and glutamine levels in the mid-prefrontal cortex of mice (Son et al. 2018). Spinach has shown neuroprotective effects on aging rats by enhancing cognition and motor skills. So based on the current research study, spinach can be used in a therapeutic strategy for ScZ patients. However, a more detailed and comprehensive preclinical study is needed (Gorelick et al. 2020).

10.7.7 Embelin

Embelia ribes is used for different psychiatric disorders in India and is capable of treating depression (Gupta et al. 2013). It consists of multiple properties like cardioprotective, anti-anxiety activity, etc. (Caruso et al. 2020). Uzbay et al. (2013) have established that embelin shows positive results by reducing seizures and enhancing cognitive behavior in zebrafish. Based on these properties, it can be

used for the treatment and management of ScZ as it has given positive results in vivo studies which are mentioned in Table 10.1 and shown in Fig. 10.2.

10.7.8 Emodin

Emodin is an anthraquinone compound found in plants like aloe vera. Emodin consists of multiple properties like anti-inflammatory, antioxidant, antimicrobial, anticancer as well as hepatoprotective properties as well. Peng et al. have shown the antidepressant effects of emodin on rats (Cui et al. 2020). Emodin is used for multiple diseases such as AD, PD, anxiety, depression, and ScZ (Mitra et al. 2022). It shows a positive effect in the animal model of ScZ, so it can be used for ScZ management.

10.7.9 Stigmasterol

Stigmasterol is found in multiple vegetables like cabbage and also in nuts, seeds, etc. It has the potential to cross the blood–brain barrier. It acts as a memory enhancer with antioxidant, anti-inflammatory, and neuroprotective properties. The properties of stigmasterol are effective in the treatment and management of ScZ (Yadav et al. 2018). It has shown positive results on animal models of ScZ which is mentioned in Table 10.1 and Fig. 10.2 of this chapter.

10.8 Conclusion and Future Challenges

Schizophrenia involves a range of symptoms, and these usually tend to overlap with several other psychotic disorders. It requires an early diagnosis and treatment to subside the symptoms to a certain level if not completely dismiss them. The diagnosis can be performed through multiple physical exams and evaluations for any present unusual thought patterns, delusions, and drug abuse symptoms, and the ultimate diagnosis is performed based on the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V). Non-medicinal treatments such as various social or vocational therapies can be performed individually or in combination with the medications used in the treatment regime. Over the past years, numerous such antipsychotics, as stated in the chapter, have been identified. These drugs are categorized as a part of the therapeutic strategies for the treatment of ScZ. These are usually present in the environment (both in the marine and terrestrial worlds) and can be extracted to generate efficient antipsychotics which play a potential role in the treatment of ScZ. Further research is needed to determine superior antipsychotics among the available ones, their precise properties, disadvantages, and the optimal

Table 10.1 The outcomes of different therapeutic approaches tested on various animal models of schizophrenia

Therapeutic approach	Animal model	Method used (with dosage)	Results/outcome	References)
Clozapine and haloperidol	Mice	To observe expression of SNAP 25 based on glutamatergic hypothesis on mice Induced saline for 5 days followed by MK 801 (NMDA antagonist) at (0.3 mg/kg/day) then clozapine (5 mg/kg/day) as well as haloperidol (1 mg/kg/day)	Haloperidol has no effect on level of SNAP 25 which show better result than clozapine as clozapine increases hippocampal SNAP25	Homayoun and Moghaddam (2007)
Risperidone, haloperidol, and aripiprazole	Gunn rat	Prepulse test inhibition (PPI), social interaction test, and open field test	Imitate cognitive defects and negative symptoms and Gunn rat strengthen the result for further research of all three mentioned antipsychotics	Tsuchie et al. (2013)
Clozapine	Rats with Post-weaning social isolation stress (PWSI)	Post-weaning social stress to rats for 8 weeks and divided into three group and induced clozapine at 2.5 mg/kg/day for 28 days and non-treatment subgroups	Chronic treatment of clozapine improves behavioral as well as immune inflammatory response in prefontal cortex by attenuating PWSI	Amiri et al. (2021)
Sodium nitroprusside (SNP)	Sprague Dawley rat model	Induced dizocilpine MK801 (0.4/kg) in rat and Y maze test, prepulse test, prepulse migration, rotarod test	SNP failed to show positive effect on ScZ-like symptoms induced by MK801	Wang et al. (2019)
Haloperidol (HAL)	Rat	HAL given at (0.05 mg/kg/day) and amphetamine was induced, and similar reduced low dose was used	When post-mortem neurochemical analysis of brain was performed, there is altered monoamine levels in few brain regions and cognitive deficits when dose was reduced	Gao and Li (2014)
Minocycline	Gunn Rat	Prepulse inhibition and novel object recognition test was performed	Minocycline shows positive in Gunn rat by atteuning microglia activation as well as enhance memory	Liaury et al. (2014)

(continued)

Table 10.1 (continued)

Therapeutic approach	Animal model	Method used (with dosage)	Results/outcome	References)
Melatonin	Pinealectomized (Px) and ovariectomized (Ovx) rats	Melatonin at dose of 5 mg/kg/day was induced for 28 days after 5 months of sham ovariectomy and prepulse inhibition (PPI) and locomotor activity accessed	Melatonin shows positive effect in impairment on PPI reflex in Px and Ovx rats	Uzbay et al. (2013)
Melatonin	Swiss albino mice	Three different groups ($n = 6$), MK 801 (1 mg/kg/mL, i.p), open field, rota rod, grip strength, and elevated pulse maize	Melatonin shows protective effect on prefrontal cortex and reduced elevation of AChE	Andrabi et al. (2019)
Melatonin	12-week-old rats of 6 groups of ten each	Y maze, open field, elevated pulse maize was performed in which first ketamine was used at 15 mg/kg for 10 days and before commencement of 14 days haloperidol/olanzapine/melatonin induced	Ketamine shown negative result in all behavioral test and after inducing melatonin symptoms reduced	Onaolapo et al. (2017)
Cannabidiol (CBD)	Wistar rats and spontaneously hypertensive rats	CBD induced in rats between 30 and 60 post-natal days in which dose was 0.5, 1 or 5 mg/kg in which locomotor activity, social interaction, fear, and prepulse inhibition of startle was assessed	CBD show positive result on cognitive symptoms	Peres et al. (2018)
Delta 9-tetrahydrocannabinol	Sub-chronic phencyclidine (PCP) rat model	Motor activity test, social interaction, and elevated pulse test to observe behavior of PCP treated rat in which Delta 9-tetrahydrocannabinol given at 0.1, 0.3, 1.0 mg/kg i.p	At low dose, Delta 9-tetrahydrocannabinol shows positive result on ScZ rat model but not effective at high dose	Seillier et al. (2020)
Omega 3 fatty acid	Young Wistar rats (30 days old)	Ketamine was induced in Wistar rat to cause ScZ followed by omega 3 fatty acids and animals sacrificed and Wistar rat brain used to measure AChe activity and gene expression	Omega 3 fatty acid shows positive result by reducing acetylcholine level in Wistar rats' brain	Zugno et al. (2015)

Curcumin	Mice with six animals in five different group	Scopolamine induced cognitive impairment and curcumin was induced at 100 mg/kg i.p for 28 days followed by behavioral test like elevated plus maze test and spontaneous behavior alternation as well as Ache level and nitric oxide level was also measured	Curcumin improved cognitive impairment as well as reduce acetylcholine and nitric oxide level	Khan et al. (2020)
Embelin	Albino Wistar rats and Swiss albino mice of 150–220 g and 25–30 g respectively	Apomorphine was induced in mice to observe climbing behavior and stereotyped behavior in rats. First embelin was given at dose of 5 and 10 mg/kg for one time for 15 days before apomorphine	Embelin show positive result at dose of 10 mg/kg and can be used for psychotic disorders like SCZ	Durg et al. (2017)
Stigmasterol	Male Swiss albino mice	Ketamine was induced and locomotor activity, stereotypic behavior was assessed	Ketamine helped in the management of psychosis symptoms	Yadav et al. (2018)

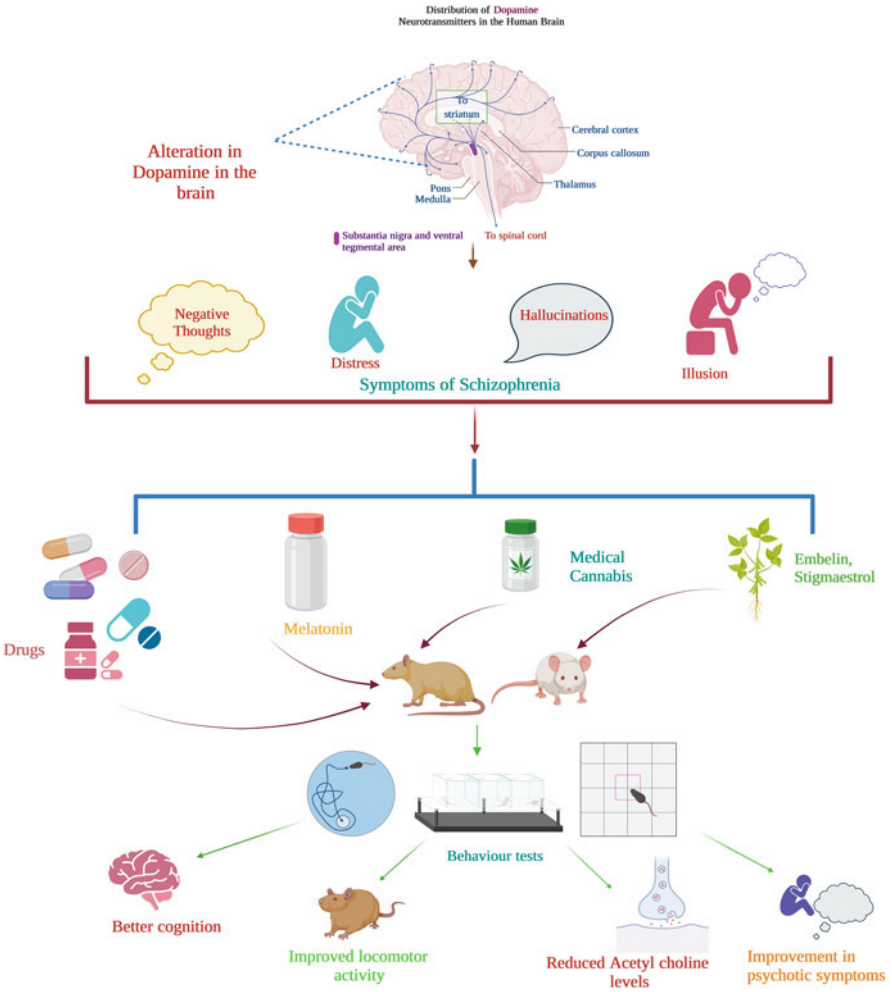

Fig. 10.2 Disturbances in Dopaminergic Neurotransmission Is Seen in Schizophrenia. Alternations in this pathway lead to ScZ in which hallucination, illusion, dilution, negative thoughts are major primary symptoms. For the management of symptoms and treatment of ScZ, mainly antipsychotics and melatonin, medicinal cannabis, and herbal products/extracts like embelin are used. Ongoing preclinical studies for melatonin and medical cannabis differ, and for antipsychotics, as most of the antipsychotic show weight gain as adverse effect. When such treatment approach is tested on animal models (like mice and rat), the behavioral studies show positive results displaying improved cognition, locomotor activity with reduction in acetylcholine levels as well all major symptoms are also reduced

doses required to administer to patients without causing voluminous side effects. Moreover, the emerging medicinal compounds/agents like curcumin, emodin, stigmasterol, spinach (Spinacia oleracea), vitamins, exogenous melatonin, and cannabidiol, all have been shown to improve the symptoms associated with

schizophrenia. However, more studies are required to elucidate the mechanism of action and potential adverse effects if any associated with these compounds.

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Chapter 11
Alternative Therapies Used in Schizophrenia

Tamara Hummadi

11.1 Introduction

11.1.1 History of Previous and Conventional Therapy for Schizophrenia Psychiatric Disorder

Overtraining at a clinical school and specialization in neuropsychiatry, different books, which were utilized by understudies during their investigations, noticed that mental problems are treated by various organic and socio-helpful techniques. In many years, "the cutting edge psychiatry" has presented natural medication and profound treatment for the treatment, while lately, doctors have frequently referenced other options and integral strategies in treating mental issues, including schizophrenia (Kaplan and Sadock's 2007). Moreover, in the most recent published work of the American Psychiatry, "Abstract of Psychiatry," a specific section named which implies "Correlative and Elective Medication in Psychiatry" expounds and depicts close to 45 other options and integral strategies in the treatment of mental problems.

Schizophrenia is related to severe social and mental malady (Lewis and Moghaddam 2006; Stanghellini and Ballerini 2007). Customary medicines for schizophrenia, including antipsychotic prescriptions (Kapur and Mamo 2004), may not dispense with all side effects and have the potential for unfavorable impacts (Stahl and Buckley 2007). Drugs, which some call an elective medication or an alternative in today's world, are as old as humankind, while the composed documentation on medicines goes back over six millennials. Old Asian and Theban, Nubian history overflows with records of regular medication—from spices to needle therapy medicines, giving important information to an individual's medical care

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even today. For millennia, just normal cures and elective techniques were accessible to individuals for treating different mental issues.

Alternative therapies are presently a term that suggests different medicines, except regular, for example, formal, customary medicine (tablets, syringes). Earlier research has recommended that patients with psychiatric problems go to vital and elective medication, characterized as items and practices that are not viewed as a feature of traditional clinical practice that is globally accepted (Public Organizations of Wellbeing 2009). Past investigations recommend that the regular accepted and alternate medication is principally utilized notwithstanding regular treatment (Demling and Worthmuller 2002) by people looking to work and make better their well-being (Rickhi et al. 2003) and to reestablish the trust that their pain might be decreased if not disposed of (Murray and Rubel 1992). Nonetheless, the clinical advantages of alternative therapies and its complimentary for maniacal side effects are either unverified (Ping et al. 1997) or have been discredited (Chen et al. 1997; Rathbone et al. 2005; Zhang et al. 2001).

For this sort of treatment, a superior term is correlative, which supplements the cutting-edge medication in methods of medicines, led by various standards whose outcomes and achievements are evident. After the ascent of drug industries recently and considerable advancements in the treatment, a time of dissatisfaction comes in tolerating how manufactured medications are not all-powerful. Because of this reality, there has been a developing interest somewhat recently in the treatment of mental and psychiatric problems, including schizophrenia, by utilizing option and integral techniques.

11.1.2 Alternative and Complementary Therapies to Schizophrenia

Alternative therapies are a terminology regularly used to incorporate all the recuperating practice that do not fall inside or is classified under the domain of traditional medication. It tends to be characterized as an assortment of restorative or preventive medical services practices, like pseudoscientific naturopathy, chiropractic, natural medication, and homeopathy that do not follow commonly acknowledged clinical techniques and might not have a logical clarification of their viability.

Correlative and alternative therapy is the interchangeable word for clinical items and practices that are not a piece of standard consideration and care. Standard consideration or care is what clinical specialists, specialists of osteopathy, and partnered well-being experts, like enlisted medical caretakers and actual advisors in the form of therapists, do. Integral medication implies conventional medicines that you use alongside standard ones.

Alternative therapies particularly differ from reciprocal medication, which is intended to go with, not supplant and replace, clinical practices. The local clinical

area does not perceive alternative clinical practices as standard or ordinary clinical methodologies.

Complementary and Alternative Medicine (CAM) alludes to types of medical care that are utilized, moreover (correlative) or rather than (alternative) conventional clinical therapy. Reciprocal treatments are, in many cases, in light of conventional information. The logical proof proposes that some correlative well-being approaches might assist individuals with overseeing constant agony. In many examples, how much proof is excessively little to show whether a specific treatment is compelling for everybody. There is less logical proof accessible about their security and adequacy than regular medicines for assessing and managing pain.

In the countries of the West, reciprocal or complementary medication strategies or methods are utilized in severe ailments with the assumption of a positive outcome in mitigating the sickness. For instance, Reiki utilized in Japan is a correlative medication item with an upper impact.

It has been proven that generally speaking, where drug treatment is not liked, the medication utilized is not all around endured, or these specialists are ineffectual, reciprocal medicines have been viewed as successful in various degrees. S-Adenosylmethionine is one of the favored regular items for the treatment of mentally depressed individuals.

The most-utilized reciprocal medication strategies to treat rest aggravations (restlessness at night) and memory issues include Melatonin, Valeriana officinalis, and Kava. For shortfall hyperactivity jumble, psychostimulants are the principal drug treatment, and different non-drug correlative medication techniques are suggested close by drug treatment or independently.

By current writings, journals, and logical information in the form of research data, no complementary or reciprocal medication technique can alone supplant pharmacotherapy regarding its viability and unwavering quality. Be that as it may, fundamental unsaturated fats and exercise utilized with psychosocial intercessions alongside drug treatment have shown trust. It has been seen that omega-3 unsaturated fats and amino acids utilized notwithstanding pharmacological treatment are compelling in the effective treatment of burdensome time of bipolar issue, yet are lacking in hyperperiods.

Likewise, it has been observed that homegrown medicines are more powerful in letting side effects free from the burdensome period. There are concentrates which show that magnesium utilized as a mineral enhancement diminishes the recurrence of hyper backslide and the seriousness of the hypersymptoms.

The utilization of Customary and Complementary Medication (CCM) is broader than, for the most part, thought. This expands the meaning of incidental effect, appearance, and collaborations connected with drug and CCM accompanying use.

Notwithstanding, CCM does not have a good spot in the clinical preparation educational program. As well as bringing issues to light about CCM among doctors, research on this theme can direct administrators in the errand of deciding forthcoming well-being arrangements. Studies have been done on the recurrence of the purpose of CCM and its significant attributes in different pieces of the country.

Large numbers of the reciprocal methodologies read up for ongoing agony have outstanding well-being records. However, that does not imply that they are sans risk for everybody. Numerous things should be thought of as preceding utilizing any CAM treatment like an individual's age, current well-being status, presence of other ailments, or pregnancy. Another significant thought is taking recommended or over-the-counter drugs, as these may influence the security of a few correlative methodologies.

Assuming you are thinking about or involving a reciprocal methodology for torment, you want to check with your medical care supplier to ensure that it is ok for yourself and is viable with your ordinary clinical therapies. A few spices and traditional medicines can collaborate with different drugs and prevent them from working appropriately. They can likewise cause aftereffects. Consequently, this study asks the utilization of integral medication techniques and treatment for psychiatry patients and their apparent degrees of adequacy and proficiency.

11.1.2.1 Examples of Alternative and Complementary Medicine Therapy for Schizophrenia

11.1.2.1.1 Complementary Dietary Plan and Use of Herbs

Brown et al., in his publication and research, found that the eating regimens of schizophrenia patients contained more all-out fat and less fiber than the eating regimens of a benchmark group matched for age, orientation, and training, albeit the admission of unsaturated fat was viewed as comparable in the two gatherings. In another review, McCreadie et al. (1998) concentrated on the dietary admission of 30 people with schizophrenia living in helped living offices in Scotland and a benchmark group matched for sex, age, smoking, and work status. Most people with schizophrenia were overweight or fat, and immersed fat admission was higher than suggested in the weight control plans for people with schizophrenia (Gothelf et al. 2002). It was found that people with schizophrenia consumed less absolute fiber, retinol, carotene, L-ascorbic acid, vitamin E, organic product, and vegetables than the benchmark group.

McCreadie (2003) concentrated on dietary propensities for 102 people with schizophrenia with extraordinary accentuation on products of the soil admission and smoking way of behaving. The review presumed that the patients (mainly male patients) had unfortunate dietary options. Graham et al. proposed that regulating vitamin D in people with schizophrenia enhances their pessimistic side effects. In one more concentrate by Strassnig et al. (2005), the dietary propensities for an aggregate of 146 grown-up local area abiding people with schizophrenia were examined. It was seen that the patients devoured a higher amount of food that incorporates protein, sugar, and fat than that of a benchmark group. Such propensities can prompt cardiovascular sicknesses, type II diabetes, and fundamental aggravation in people with schizophrenia. These sicknesses are connected with a short life expectancy in people with schizophrenia. In an examination concentrate by Joseph

et al. (2017), it has been proposed that high-fiber diets can work on the resistant and cardiovascular framework, accordingly forestalling untimely mortality in schizophrenia.

11.1.2.1.2 Ginkgo-Ginkgo Biloba

The delegate of the Ginkgoaceae family was the one in particular that endured the ice age and the nuclear bomb in Hiroshima. It has been highly famous in Western medication, and it got the name "the remedy for the apprehension about maturing." The dynamic substances are glycosides (bioflavonoids), solid cancer prevention agents that may dial back blood thickening, and glycolides that further develop blood course and defensively affect neurons (Kulier 2000).

It mitigates or kills the side effects of wooziness, cerebral pain, memory inadequacy, absence of fixation, sleep deprivation, testiness, sensations of nervousness, and dread (Itil et al. 1996). It is additionally utilized in the treatment of dementia, melancholy, wooziness, headache, and feebleness with vascular kinds. In a mix with standard antipsychotics, it is suggested for schizophrenia. There are concentrates that show further developed viability and diminished extrapyramidal secondary effects. The typical portion is 360 mg/day (Olson 2000).

11.1.2.1.3 Cognitive Behavioral Therapy (CBT)

Cognitive behavioral therapy (CBT), otherwise known as mental conduct treatment (MCT), is a remedial strategy that changes the unfortunate method of reasoning, feeling, and conduct. MCT includes reasonable self-improvement methodologies, which are found to enhance positive side effects in schizophrenia. MCT joins two treatments: "mental treatment" and "social treatment." The blend of these two strategies frequently empowers the patient to have solid considerations and ways of behaving.

A writer, Morrison sums up the utilization of MCT in people with schizophrenia to address the essential side effects of the disease and friendly debilitations. He referenced that numerous schizophrenia side effects are impervious to pharmacological treatment and proposed MCT as an extra to antipsychotics can be more successful than the organization of medications alone. For instance, a few examinations found that mental recovery and MCT can improve mental shortages and thus sure side effects (Morrison 2009).

There are numerous procedures to modify contemplations and conduct utilizing MCT. One examination concentrate depicted the critical components of MCT for schizophrenia (Tai and Turkington 2009) and reasoned that different MCT methods can be utilized really in schizophrenia. One of the methods, known as mental rebuilding, incorporates provoking the patient to concoct proof to demonstrate that their convictions are genuine. This strategy helps the client to understand that they have dreams. This procedure helps the patient figure out how to recognize and

challenge negative considerations and change the flawed contemplations with additional practical and positive ones. MCT was likewise observed to be powerful for overseeing vagrancy.

As MCT enhances mental weakness, it further develops a relationship and contributes emphatically to amusement. Conduct treatment plans to help the patient figure out how to adjust their behavior. For instance, they might practice conversational abilities to involve these recently acquired abilities in friendly circumstances. MCT helps the patients in taking part in groups of friends which influences kinship and relationship.

There have been approved investigations of MCT in schizophrenia throughout recent years. In schizophrenia, MCT is one of the most usually involved treatments in the UK (by and large, notwithstanding prescriptions). MCT has been suggested as a first-line treatment by the UK public well-being administration (NHS) for people with schizophrenia. Likewise, the American Mental Affiliation (AMA) proposed MCT for people with schizophrenia.

MCT was additionally observed to help lessen confused conduct, which influences day-to-day living in people with schizophrenia. In one exploration concentrate by Wykes et al. (2008) in the US and Joined Realm, it has been observed that MCT is more liked than other conducted treatments. This study shows that MCT enhances positive side effects, disposition, and social nervousness. Notwithstanding, there was no impact on misery.

MCT here and there remembers the group of the patient for treatment meetings, which is why the patient and their vocations generally welcome MCT. MCT brings the patient and their vocations into a cooperative climate as a piece of the treatment group and urges them to take an interest effectively in treatment. It has been observed that mind flights, daydreams, negative side effects, and wretchedness are likewise treated with MCT (Sensky et al. 2000).

MCT includes doing schoolwork which permits the patient and their career to mitigate the upsetting side effects of schizophrenia. MCT energizes taking meds consistently and coordinating with the local area. MCT has likewise been upgraded impact when joined with antipsychotic medicine, contrasted with the organization of prescriptions alone.

11.1.2.1.4 Yoga and Physical Activities Treatment

Yoga treatment can likewise oversee schizophrenia side effects, frequently in mix with pharmacological prescriptions (Jha 2008). Pharmacological mediation alone probably will not create every one of the advantageous results in overseeing schizophrenia side effects, particularly bad side effects. As an extra to antipsychotic meds, yoga helps treat both positive and negative side effects, more than prescriptions alone. Moreover, pharmacological intercessions frequently produce weight in schizophrenia (Gangadhar and Varambally 2012).

Yoga treatment has been found to decrease weight gain because of the organization of antipsychotic prescriptions. Pharmacological mediations could cause

endocrinological and feminine brokenness, which might be emphatically treated by yoga treatment. In an examination concentrate by Gangadhar and Varambally (2012), two gatherings of patients on antipsychotic meds were analyzed. In one gathering, yoga treatment was managed. In the other gathering, a bunch of actual activities was applied. The two gatherings were prepared for a multimonth (something like 15 meetings). The yoga bunch showed preferable negative side effect scores over the other gathering. Essentially, yoga treatment improved impacts on friendly brokenness more than the other gathering.

Thusly, Vancampfort et al. (2012) found that rehearsing yoga diminishes mental side effects and works on psychological and actual personal satisfaction and decreases metabolic gamble.

The most likely clarification of the viability of yoga treatment is the development of oxytocin in the body. Oxytocin is a chemical which adds to prosperity. In one examination study, 50 patients were controlled oxytocin alongside antipsychotic prescriptions. It was found that both negative and positive side effects worked on in those patients. The consequences of yoga treatment are manifolds. Yoga treatment can prompt a decrease in insane side effects and gloom, improvement in cognizance, and an expansion in the nature of life (Feifel 2011).

11.1.2.1.5 Integrative Psychiatry

Another sort of integrative psychiatry specifically integrates components of reciprocal and elective medication into training strategies (Kaplan and Sadock's 2007). Contingent upon the kind of schizophrenia, its stage, or articulation of sequelae in a reduction stage, the desires and needs of every patient, the social qualities of the climate in which the person in question lives ought to be thought of. It is attractive in a phase of the sickness to suggest some type of correlative treatment. Surely, there is an enormous number of patients for whom the cutting-edge medication techniques and recorded complementary strategies may likewise help, for example, an eating regimen and healthful treatment, homegrown treatment, manipulative treatment of some sort, or for instance, lively treatment. It positively cannot be unsafe on the off chance that an appropriately treated schizophrenic patient goes to bioenergetics rub and takes specific natural medication or a multivitamin item. There is developing proof that this sort of integral treatment helps.

11.1.2.1.6 Music Therapy

Music treatment alone affects the general improvement of positive side effects and parts of fancies, unusual ways of behaving, and formal reasoning. As to side effects, music is more powerful in working on the subscales of avolition and alogia than other adverse side effects. Music works on the patient's way of behaving, makes it more regular, and works on their relationship with the climate (Khalaf-Beigi et al. 2012).

Music treatment can assist individuals with schizophrenia work on mental state (general side effects, wretchedness, and tension), general and social working, worldwide state, and personal satisfaction in the short to medium term. Music treatment especially appears to influence patients' inspirational, close to home, and social angles and assists patients with working on their social exercises and related jobs. Music treatment integrates music encounters to assist individuals with genuine mental issues and foster connections as they will most likely be unable to utilize words alone to take care of issues (Geretsegger et al. 2017).

Music treatment is the controlled utilization of music on individuals to help with their physiological, mental, and profound coordination during treatment. Dynamic and latent music treatment can enhance psychosis and wretchedness, including treatment-safe cases. In dormant music treatment, the specialist and patient effectively make music, utilizing instruments and voices. In detached music treatment, the patient rests, and the advisor plays music and welcomes the patient to picture quiet pictures to deliver a condition of mental restoration. Various music treatment studies have been led by clinical experts, like specialists, medical attendants, clinicians, and word-related advisors.

This shows that music treatment applies to various disciplines in medication. Music treatment is a sort of psychotherapy that utilizes melodic collaboration and correspondence. An investigation of music treatment for schizophrenia distinguished five randomized control preliminaries that qualified for meta-examination. This study analyzed the impacts of music treatment over the short to medium term (1–4 months), with treatment courses changing from six to 80 meetings. The music treatment joined with standard consideration is better than standard consideration alone. It assists individuals with schizophrenia work on their worldwide state and may work on their psychological state and working assuming adequate music treatment meetings are given. Studies have presumed that further examination should investigate music treatment's drawn-out impacts and portion reaction connections.

A few investigations and critical analyses have detailed that music treatment is a successful mediation for schizophrenia. A study (Talwar et al. 2006) utilized a particular music period or session treatment, and one more arrangement of four utilized bunch of music mediations. Patients were hospitalized, including schizophrenia patients. The music therapy sessions, which involved tuning in, examining, singing, and instrument playing, lasted for 3–4 months. The estimation instruments utilized in these examinations incorporated the scale for evaluating adverse side effects, the positive and negative disorder scale, and the short mental rating scale.

The outcomes demonstrated how music mediation could fundamentally further develop schizophrenia side effects, negative side effects, and personal satisfaction. All reviews led to pretests and posttests. One of the examinations additionally led to a subsequent test following 4 months.

Indonesia, for instance, has a deficiency and an inadequacy of music specialists in clinical organizations; the nursing staff is commonly answerable for advancing music treatment exercises. Music treatment can improve patients' satisfaction with severe and long-haul psychological maladjustments (Bloch et al. 2008). Be that as it

may, no review has investigated the impacts of music treatment on schizophrenia patients in a mental nursing home setting.

11.1.2.1.7 Multivitamins and Supplements

Multivitamin items for most of patients experiencing schizophrenia it is prescribed to utilize multivitamin items because of their horrible eating routine. Individuals do not create nutrients—vitamin D is a special case—and they should be taken from an external source to take care of the mind and different organs appropriately. The nutrients play an integrative part in the working of the sensory system.

They assist the cerebrum in the union of synapses, which affect the state of mind and judgment and can be valuable in treating schizophrenic patients. L-ascorbic acid assumes a significant part in the blend of a norepinephrine synapse, and synapses are of basic significance for the mind and can influence conduct. L-ascorbic acid is additionally an exceptionally powerful cancer prevention agent. Vitamin E settles the greasy layers in the cerebrum and shields it from harm through the arrangement of free revolutionaries in cells. Along these lines, it dials back the deficiency of mental capacities.

11.1.2.1.8 Glycine

A few investigations show that little amino corrosive glycine builds the movement of synapses and lessens the negative side effects of schizophrenia when utilized with antipsychotic treatment, particularly with haloperidol and perphenazine (Waziri and Baruah 1999). In the treatment of schizophrenia, the suggested portion is between 45 and 95 g each day (Kaplan 2008).

11.1.2.1.9 Mental Improvement Treatment (MIT)

This sort of treatment is additionally called mental remediation. It shows individuals how to all the more likely perceive expressive gestures or triggers and work on their consideration, memory, and capacity to sort out their viewpoints. It joins computer-based mind preparation and meetings in group. It is a complete, formative way to deal with the remediation of social and non-social mental shortages in schizophrenia that tries to work with the improvement of grown-up friendly mental achievements (e.g., point of view taking, social setting evaluation) by moving reasoning from dependence on effortful, sequential handling to a "topic-filled" and unconstrained reflection of social topics.

The treatment comprises roughly 80 h of the system helped and aided neurocognitive preparation in consideration, memory, and critical thinking; and close to 60 social–mental gathering meetings that utilize in vivo growth opportunities to encourage the advancement of social insight and outcome in relational

collaborations. An expansive, hypothetically determined cluster of social–mental capacities are focused on in the social–mental gatherings, which range from abstracting the "substance" or central matter in close associations to the point of view taking, social setting evaluation, and feeling management (Selman et al. 1990).

11.1.2.1.10 Composed Specialty Care (CSC)

This is for individuals encountering an episode of psychosis interestingly. It is a group approach that consolidates medicine and mental treatments. It incorporates social and business administrations and attempts to include the family whenever the situation allows. The point is to alter the course and anticipation of the illness by getting it in its earliest stages. Research shows that individuals with schizophrenia who seek early and concentrated treatment have the best long-haul results.

11.1.2.1.11 Family Interventions

Family intervention has been widely investigated and will more often than not range from customary family treatment to psychoeducational treatments. In light of this exploration, there is proof for a scope of advantages of family treatment in the first episode of psychosis and more development phases of ailment, like expanded medicine consistency and diminished hospitalization and backslide. Notwithstanding, adequacy of family treatment in the in danger mental state is yet to be laid out and a gathering of us analysts is presently testing this. This is particularly significant given that patients in the in danger mental state and first episode of psychosis will quite often have more noteworthy collaboration with their families contrasted with patients with a constant course of the issue who are by and large more seasoned, and that implies that the impact of family treatment right off the bat in the ailment might be more grounded.

11.1.2.1.12 Vocational and Social Skill

Work can be a "normalizing" experience and give advantages like improved individual fulfillment, expanded confidence, extra pay, monetary autonomy, social connection, and sporting and friendship open doors. Above all, it is regularly recognized as an objective of individuals with schizophrenia. Any individual with schizophrenia who communicates an interest in acquiring business or who might profit from work ought to get professional administration.

11.1.2.1.13 Electroconvulsive Treatment (ECT)

In this strategy, terminals are joined to the individual's scalp. While under broad sedation, specialists send a slight electric shock to the cerebrum. For the most part, a course of ECT treatment includes less than four doses each week for quite some time. Each shock treatment causes a controlled seizure. A progression of medicines after some time prompts perking up and thinking. Researchers do not completely see precisely how ECT and the controlled seizures it causes help, albeit a few specialists imagine that ECT-actuated seizures might influence the arrival of synapses in the cerebrum. It, however, helps when medications cease to work or, on the other hand, assuming extreme melancholy or mental shock makes treating the sickness troublesome.

11.1.2.1.14 Psychosocial Treatments

Psychosocial treatments have been intended to help practical recuperation by focusing on regions involved in the advancement of inability, for example, impeded social and job working, however, which are not straightforwardly connected with side effects of ailment. They have been accounted for to develop treatment adherence further and advance better word-related and social working in laid out schizophrenia.

Considering that schizophrenia ordinarily happens in late puberty and early adulthood, which are basic periods of life for social and word-related improvement, these working areas are often the first to show checked decline from premorbid levels. Regardless of needing to remain at the everyday schedule, close to half of individuals in early schizophrenia are out of the everyday schedule.

It is currently broadly acknowledged that utilitarian recuperation is similarly basically as significant as suggestive recuperation. Utilitarian inability is the most exorbitant part of insane sickness, and useful recuperation is esteemed by patients above suggestive recuperation. Treatments like professional restoration, including the return to reading up for more youthful patients, have been intended to limit useful handicaps and work on long-haul word-related work.

The most proof-based model of professional recuperation extensively and upheld business explicitly is the Singular Situation and Backing model. Investigations of it in early schizophrenia have detailed accomplished business or training rates high. Nonetheless, keeping up with word-related jobs has been distinguished as a test in this accomplice recommending that different elements, like mental capacity, are associated with effective professional rehabilitation. Thusly, there are currently suggestions for adjunctive intercessions to professional treatment to improve its belongings.

Intelligence of the mechanical turns of events and their utility in different areas of well-being, web and portable-based treatments are being created for treatment conveyance in all phases of schizophrenia. Considering that youngsters are among the most remarkable clients of these innovations, it is instinctive that intercessions are going to these assets for help.

Starter research around here has found beneficial impacts of PC and cell phones put together psychoeducation concerning the pace of backsliding, hospitalization, socialization, and prescription adherence of patients with laid out schizophrenia. Another influx of examination on web-based treatments is in progress. A new report by our gathering has demonstrated it to be practical and gainful concerning apparent social connectedness and strengthening.

11.1.2.1.15 Antipsychotic Medications

Antipsychotic sedates likewise assist with improving bewildered conduct in everyday life. They are similarly used to work on mental weakness, which further develops relationships and adds to the fulfillment of training and business. Antipsychotic drugs assist with working on muddled conduct in everyday life. They are likewise used to further develop connections and improve training and work (Omori et al. 2013).

Most antipsychotic drugs improve mind flights and daydreams, while an endeavor to likewise address the negative side effects of schizophrenia. Antipsychotic drugs are generally the main choice for the treatment of schizophrenia. A large portion of antipsychotic medicines work by lessening the positive side effects of schizophrenia by hindering dopamine receptors.

In one exploration by Girgis et al. (2002), 200 people with schizophrenia were randomized to clozapine or chlorpromazine treatment for 3 years. The adherence to clozapine was viewed as higher than that of chlorpromazine. In one more review led on 45 people with schizophrenia, it was observed that there was no beneficial impact of clozapine over ordinary antipsychotics.

Over the most recent 20 years, we see a developing revenue in non-pharmacological treatment for schizophrenia generally because of the powerlessness to accomplish total recuperation with antipsychotic drugs alone and the high announced paces of prescription non-adherence (Lacro et al. 2002). In any case, non-pharmacological treatment is inadequately utilized in clinical practice (Leucht et al. 2009).

There is some proof that non-pharmacological medicines conveyed to individuals with schizophrenia who were taking negligible portions of antipsychotics or no antipsychotics could have similar positive results as the people who take standard/typically endorsed dosages antipsychotics (Cooper et al. 2019).

Non-pharmacological medicines conveyed to people determined to have schizophrenia center around the broad scope of results like instruction, clarification, appraisal, support, reality support, building fixation, working with connections and correspondence, managing testing conduct (e.g., self-hurt, hostility), treating non-insane side effects (e.g., temperament unsettling influence, nervousness), expanding abilities of individuals with schizophrenia in their everyday existence association, and working with their families.

11.1.2.1.16 Acupuncture

Scientists recorded a contextual investigation wherein needle therapy worked on everyday capacities, rest and diminished torment, despondency and unsettling mental influences because of mind flights. This most recent exploration is supported by extra examination finding that needle therapy reduces both schizophrenia and the symptoms of mental prescription.

Investigating this latest exploration, a 70-year elderly person experienced constant visualizations of a bird "pecking his back." He encountered actual agony because of these mind flights. The mind flights continued, yet the patient "felt less upset by them." The aggravation and melancholy, in any case, diminished altogether. This was achieved in 14 needle therapy medicines at a pace of once each week for three-and-a-half months. A three-and-a-half-month post-treatment follow-up recorded enduring outcomes.

The mucus heat influencing the heart and mind allude to a physiological cycle by which psycho-emotional aggravations happen. In conventional Chinese medication, needle therapy and homegrown medication are often used to re-balance interior medication's actual awkward nature to treat these introductions of schizophrenia. Schizophrenia is treated as a physiological unevenness bringing about a state of mind instead of just a segregated mental problem separated from biophysical processes.

One more review distributed in The Diary of Mind Sickness revealed that Yi Gan San's natural recipe might be useful in treating schizophrenia and neuropsychological problems since it reestablishes cerebrum glutathione levels. In one more review distributed in Neuro-Psychopharmacology and Natural Psychiatry, analysts presumed that Yi Gan San is a serotonin modulator and is a "protected and helpful" equation for treating the social and mental side effects of dementia marginal behavioral condition. The concentrate likewise shows critical upgrades in tardive dyskinesia, psychosis, and schizophrenia.

11.1.2.1.17 Religious Beliefs and Conviction

Religious conviction through the job of healers stands apart as a type of psychotherapy connected with adherence to sedate treatment, affecting the psychopathology and psychoeducation of these patients (Aziz et al. 2016). Psychoeducation is an indicator of prescription adherence.

11.2 Conclusion

An assortment of treatments presently exists for schizophrenia going in scope from further developing side effect profiles to practical recuperation. There is decent reasoning for their utilization right off the bat throughout sickness. Such treatments

in early schizophrenia are subjectively not the same as forestalling future instances of the problem or from early side effects recognizable proof, yet may by and by assisting with diminishing dreariness in the people who go on through to the more constant course. Joining treatments, for example, mental or psychosocial with novel pharmacological medicines is a methodology that should be assessed further as various medicines, arrangements, and lengths of treatment might be required for supported benefits. Longitudinal subsequent examinations propose that the more significant part of treatment that helps right off the bat throughout schizophrenia are found in the initial 3 years and is not supported at the long-term follow-up. It is possible that a blend of longer mediations controlled longitudinally over the ailment course and as a piece of standard treatment is expected to deliver the most robust and long-haul benefits. Treatment advancement at all phases of schizophrenia is shifting from conceptualizing schizophrenia as a neurodegenerative infection with an unfortunate result to a sensible sickness. Medicines that emphasize coordinating pharmacological, mental, and psychosocial mediations, which have areas of strength for a base for viability, should be incorporated for the most obvious opportunity to turn away or upset schizophrenia. A viewpoint that early mediation can interface with existing and flawless brain adaptability components that can outfit in a versatile way to advance better brain framework working and expanded pressure flexibility, which will prompt side effect decrease and utilitarian recuperation, is turning out to be progressively well known.

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Chapter 12
Different Phases of Schizophrenia Patients: From the Psychological Perspective

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12.1 Introduction

12.1.1 History of Schizophrenia as a Psychiatric Disorder

Schizophrenia stays a mystery even though it is viewed as among the most well-known mental unsettling influences (Bromet and Fennig 1999). Its interpretation, designation, and definition have changed over time after Bleuler and Kraepelin labeled it as "schizophrenia" and "dementia praecox", respectively (Tandon et al. 2009). Kraepelin distinguished between two types of psychosis: "manic depression" and "dementia praecox." Dementia praecox (generally described as schizophrenia) was seen by Kraepelin as a natural illness caused by anatomical or toxicological mechanisms. According to Kraepelin, schizophrenia was an ever-evolving neurological condition that resulted in progressive deterioration of mental faculties. Conversely, he depicted manic depression as a rambling concern, which does not

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prompt all-time impeded mental work. Eugen Bleuler, a Swiss therapist, reexamined this idea in 1911, changing "dementia praecox" to "schizophrenia" (Ebert and Bär 2010). Amongst the most apparent differences between Kraepelin and Bleuler is that the former obtained information from patients' history, but Bleuler obtained information through rigorous clinical observations. He stayed on patients' environmental factors. Bleuler got his idea from the Greek action word schizein, demonstrating parting (Ashok et al. 2012). It has been observed that there is a very low level of awareness in people regarding Schizophrenia. This study will prove extremely helpful in filling this gap and educating people about Schizophrenia. It is very important for everyone to acquire basic knowledge about the disorder, its signs, progression, challenges, and management. Through it, suspected cases of schizophrenia will be able to get an earlier diagnosis. With lack of awareness and late diagnosis comes poor compliance and poor prognosis and vice versa.

12.1.2 Epidemiology

The occurrence and predominance of schizophrenia reveal conspicuous variety among different locations. Male manifests more schizophrenia than female (1.4:1). Transient status, metropolitan birth or home, and progressed fatherly age are related to an expanded probability of acquiring schizophrenia. Prebirth disease, nourishment is related to higher schizophrenia incidence. Schizophrenia patients having the 2-3-overlap expanded risk of mortality contrasted and everyone. This differential mortality rate might have deteriorated over the past decades (McGrath and Susser 2009).

12.1.3 Neuropathology and Psychopathology

Over 100 years ago, E. Kraepelin (1856–1926) estimated that natural irregularities of the mind happened in a disorder called praecox dementia (i.e., schizophrenia). From that point forward, experts in neuropathology field, such as A. Alzheimer (1864–1915) and many others, have studied the schizophrenia's cerebral pathology in depth. Since this period, A. Alzheimer's perception on "Psychotics (Psychosen)" is especially noteworthy. Before his milestone research on patients with dementia, he had mentioned itemized objective facts about psychotic patients' cerebral pathology. As a result, he discovered that individuals having psychotic manifestations showed no gliosis. This demonstrated that the cerebrum was not subjected to sufficiently incredible effect to induce nerve cell depletion after the brain completed development; it was neuropathologically determined that guess for such cases would be preferable to patients with dementia. It was a critical discovery with respect to the obsessive states in schizophrenia, which was termed as "presenile dementia" at that point. This finding has likewise significantly impacted current investigations planning to uncover the neurotic states of this ailment. Specifically, it affirmed that

schizophrenia etiology includes more neurodevelopmental components than neurodegeneration components. Neuropathological exploration of this illness proceeded; however, no critical discoveries apart from the shortfall of gliosis were observed. As an articulation portraying this delayed time, it was said that "schizophrenia is a graveyard for neuropathologists" (Iritani 2013). Be that as it may, since 1980s MRI, CT, and other neuroimaging methods were utilized in several instances and demonstrated schizophrenia with strange morphology of the brain, subsequently producing recharged interest in advancements inside cerebrum tissue and prompting further neuropathological research. There are currently several reports in which, notwithstanding morphological perceptions, cell distribution, and so forth are picture handled and measurably handled through PCs. Because of strategic issues in gaining ground in the cerebral pathology field, we have not yet had the option to notice sickness explicit discoveries, although there are a few discoveries with high sureness. Notwithstanding, the neurodevelopmental speculation has been upheld as having the option to make sense of the amassed discoveries of past examinations sensibly. Simultaneously, the consequences of ongoing atomic natural examinations have uncovered the probable qualities of this sickness (Iritani 2013). A few investigations show that there is a decrease in neurocognitive working before and during the beginning of this ailment. There is no persuading proof that there is an ever-evolving neurodegenerative interaction after the beginning of the sickness. We cannot give a distinct response regarding whether schizophrenia is a degenerative problem in the feeling of an ever-evolving degeneration after sickness begins (Rund 2009). At the point when the illness is going all out and side effects are serious, the individual with schizophrenia cannot perceive whether certain thoughts and discernments they have are genuine or not. This happens less frequently as they progress in age (Palazzolo et al. 2005). Positive symptoms incorporate delusions/hallucinations, voices that chat with or about the patient, and daydreams that make the patient overly anxious and paranoid. Smoothed effects, the disappearance of a sense of joy, absence of desire, and social disengagement are some of the negative side effects. Both types of side effects have an impact on patients' family; as a result, physicians need to provide guidance to everyone affected by the sickness. Intercessions from the psychosocial and family spheres can help to improve outcomes. Drugs have some control over side effects; however, for all intents and purposes, all antipsychotics make neurologic or other side impacts (e.g., diabetes, hypercholesterolemia, weight gain). Schizophrenia patients have a 10% lifetime likelihood of self-destruction (Schultz et al. 2007).

12.1.4 Genetics and Environmental (Pre- and Perinatal) Influences in Etiology

The etiology of schizophrenia is multifactorial and mirrors the cooperation between hereditary weakness and ecological triggers (Stilo and Murray 2019). Hereditary

leading factors, perinatal risk variables, and inconveniences during birth could expand the likelihood of the illness (Löhrs and Hasan 2019). There is gathering proof that prebirth contact to a wide assortment of viral and bacterial diseases or essentially irritation may unobtrusively modify fetal mental health, prompting neuropsychiatric ramifications for the youngster further down the road. The connection between flu contaminations in pregnant females and an increased incidence in the advancement of schizophrenia in their children has been portrayed (al-Haddad et al. 2019).

Multiparity, pregnancy hemorrhage, and compact size for gestational age have all been linked to a three- to four-fold accelerated chance of schizophrenia in male adults. Prespring birth was related with the expanded hazard of both schizophrenia and emotional psychosis (Hultman et al. 1999). Hallucinations and delusions are the most striking element of schizophrenia, cognitive impairment is commonly present before the beginning of psychosis and is the best indicator of the long-term utilitarian result. The impacted spaces of discernment incorporate working memory, executive capacity, learning and long-term memory, visual/hear-able insight, and consideration. Among these, the shortfalls in working memory (i.e., the capacity to fleetingly keep up with and control data for a restricted timeframe to direct thought or conduct) seem, by all accounts, to be integral to the mental impedances in the ailment, filling in as the substrate for debilitations in other mental spaces, like visual direction, memory for countenances or articles, and leader work. Together, these discoveries propose that functioning memory shortages address a central component of schizophrenia (Dienel and Lewis 2019).

12.1.5 Cognitive Functioning, and Course and Outcome

There is a wide variety in the progress of schizophrenia. Sometimes the beginning of sickness is progressive, reaching out throughout the span of months or years; in others, it can start from nowhere, inside the space of hours or days. Certain individuals have episodes of disease enduring weeks or months with full reduction of manifestations between every episode; others have a fluctuating course wherein symptoms are consistent; others again have next to no variety in their symptoms of sickness throughout the years. The ultimate result from the ailment in late life can be finished recuperation, a gentle degree of unsettling influence, or proceeding with the extreme disease. Schizophrenia typically turns out to be less extreme as the individual with the disease becomes older. Furthermore, the later the ailment starts throughout everyday life, the milder it ends up being. Females for the most part foster their first side effects of schizophrenia later than men and the course of their ailment will, in general, be less serious (Folsom et al. 2006). The drawn-out result of schizophrenia varies, contingent upon admittance to mental medical care, early recognition of psychosis, and pharmacological therapy (Volavka and Vevera 2018). The normal flow of schizophrenia was divided into three categories: gentle, medium, and extreme. Albeit a lot of fluctuation in results happened across examinations assessed,

schizophrenia is a turmoil with somewhat unfortunate results. Schizophrenia patients reliably reported more unfortunate course of events and results than individuals having other nonpsychotic and psychotic mental problems. On the upside, subcategories of individuals with schizophrenia experienced broadened times of recuperation some without the advantage of broad psychological well-being afterward therapies and schizophrenic patients did not demonstrate an ever-evolving downward spiral. Investigations looked into likewise wary us to the risk of self-destruction, early demise, and suicide in schizophrenia (Jobe and Harrow 2005).

12.2 Clinical Staging Concepts of Schizophrenia Spectrum Disorder

12.2.1 Staging Concept in Medicine

For several years, a presentation of the disease progress in terms of different phases, commonly known as "staging," has been utilized in various sectors of medicine (Agius et al. 2010). The illnesses are categorized into stages based on physiological changes, therapeutic measures, and pathological outcomes. The staging model suggests that the illness has a dynamic nature, and three conditions must be met:

- The stages should be in the increasing order of intensity of symptoms.
- The progression to the next phase should be linked to a classic clinical picture.
- Treatment is increasingly successful in the initial phases of illness (Wood et al. 2011).

The staging approach implies that this model will be used for diagnostic reasons; thus, the design of specific stages must be built on precisely described clinical, anatomical, biochemical, and physiological aspects. Based on this model, the suggested therapy can be applied sooner; it will be simpler and more productive. Furthermore, the assessment of treatment efficacy will be exact, in the clinical setting and in terms of economic burden (McGorry et al. 2007).

In the most conventional sense, staging pertains to cancer. Albert Broders, a pathologist from the United States, advocated naming cancer stages and assigning an independent prognostic rating to each one. This method has gained widespread acceptance and has evolved into the currently used classification TNM (tumor node metastasis) (Wright 2012).

Coronary artery disease is an example of how staging can be used for complete evaluation and therapy. Applying staging processes enables for a particular risk analysis of disease development (genetic predisposition, lifestyle), disease progression (e.g., metabolic disease, increased blood-pressure), as well as clinical sign extremity (e.g., angina pectoris). In conclusion, given therapy can be tailored to the particular patient's requirements as well as the stage of the illness, starting with preventative measures (diet, workout), progressing to pharmacological, and finally

surgical treatments (stents, grafts, and so on) (Hickie et al. 2013). The diagnosis and therapy efficiency of staging, as well as the ability to exchange knowledge and experience among various treatment centers, have led to a widespread use of this technique in several different fields of medicine, including the treatment of obesity or amyotrophic lateral sclerosis (Sharma and Kushner 2009).

12.2.2 Staging Concept in Psychiatric Disorder

The clinical utility of staging prompted psychiatrists to adopt the model in their fields. In psychiatry, defining strict criteria for a diagnosis for respective stages of the illness would allow distinguishing initial disease from developmental variations or regular attitudes characteristic of a particular stage of life (McGorry et al. 2010).

Implementing staging in psychiatry would help us to abandon stoicism in favor of a more advanced approach that considers environmental and genetic components and their impact on the onset and progression of disease. This is worth noting that mental disorders have become highly frequent, and that the majority of known mental disorders occur in individual aged 25 or younger, frequently advancing from initial mild problems to a full-blown psychiatric syndrome (Kessler et al. 2005). Kellner and Fava postulated using the psychiatry staging model in 1993, citing its utility in trying to describe schizophrenia, recurrent depression, and chronic anxiety (Fava et al. 2012).

12.2.3 Different Staging Concepts in Schizophrenia Spectrum Disorder

12.2.3.1 Staging Concept of Lieberman and Insel

Lieberman defines schizophrenia as having three pathophysiologic phases that are defined in four stages (Cosci and Fava 2013). The first stage would be the premorbid or neurodevelopmental stage, which starts in initial teenage years or earlier and marked by minor social and cognitive abnormalities (stage 1). The second stage is the neuroplastic phase that is further subdivided between prodromal, on set, and deteriorating sub-phases and is known as stages 2 and 3, respectively. Apart from the deficiencies indicated above, modest psychotic symptoms may be present throughout the prodromal stage, leading to complete psychosis in the start (stage 3). The neuroprogressive pathophysiological phase is termed as the residual or chronic phase, which is marked through significant negative and perceptual distortions and psychotic episodes. According to Lieberman, antipsychotic medication should be used only after the beginning of the maiden psychotic episode (Lieberman et al. 2001).

Like Lieberman, Insel defined the very same stages of schizophrenia 9 years later, although with somewhat alternative names (Insel 2010):

Stage 1: presymptomatic risk
Stage 2: prepsychotic prodrome
Stage 3: acute psychosis
Stage 4: chronic illness

12.2.3.2 The Singh Staging Concept

Singh and colleagues' staging concept is primarily concerned with the sequence of psychosis development. Their approach begins with the prodromal phase (stage 1), which has been split into two portions: a course of discomfort (P1) and nondiagnostic symptoms stage (P2). The second stage begins with the appearance of the maiden psychotic signs, which are positive manifestations like false fixed beliefs, hallucinations, etc. The third stage is an intermediate stage in which symptoms accumulate and the diagnostic picture of schizophrenia is made. When the diagnosis is confirmed, the patients enter the fourth stage (Singh et al. 2005).

12.2.3.3 The Aguis Staging Concept

The most familiar and simple idea of staging was put forward by Aguis. He divided the disease into three stages: stage 1 (prodromal stage), stage 2 (first episode), and the stage 3 (chronic phase). Agius also acknowledged that there is a premorbid period preceding the prodrome (Agius et al. 2010).

12.2.3.4 The Mcgorry Staging Concept

McGorry and colleagues proposed one of the most established and recognized schizophrenia staging models (Berendsen et al. 2020). This notion begins with stage 0, in which there is zero ongoing symptom in the patient, however, is at elevated chance of developing a psychotic condition. The first stage is split up into two substages: 1a, in which the patients present with nonspecific mild manifestations and 1b with intermediate signs. Second stage refers to the very first launch of psychosis. The third phase is subdivided into three parts, incomplete remission (stage 3a), psychotic disorder relapses (stage 3b), and numerous relapses (stage 3c). Lastly, stage 4 denotes a chronic and serious sickness. This staging concept is important because it may be applied to individuals with some other extreme disorders such as depression or bipolar disorder (McGorry et al. 2010).

12.2.3.5 The Cosci Staging Concept

Cosci et al., in 2013 introduced a general staging concept of schizophrenia (Cosci and Fava 2013). The paradigm begins with a prodromal period (stage 1) and proceeds longitudinally through the primary phases of psychiatric diseases, with second phase becoming an acute manifestation, third phase being residual period, and last phase being the chronic phase (Cosci and Fava 2013). Cosci did not include the premorbid period like McGorry and Leiberman, since there was insufficient evidence in previously conducted studies, and he claimed that it had lower clinical value because it can only be assessed in retrospect (McGorry et al. 2010).

12.2.3.6 The Fountoulakis Staging Concept

Fountoulakis and colleagues proposed a new notion of clinical staging in schizophrenia by employing the 5-factor model (built on the concept that schizophrenia can be represented through by negative, positive, hostility, affective, and cognitive manifestations) and PANSS (Positive and Negative Syndrome Scale) (Fountoulakis et al. 2019). They attempted to objectively construct a staging framework by evaluating 2358 stable patients with schizophrenia of varied age groups. They categorized the disease into four stages and provided their specific timeline.

In stage 1, the antagonism and excitement were discovered to rise with time, which lasted about 3 years, this excitement became a predominant symptom group in the second stage. Negative and stressful events were steady during the first two phases and began to grow progressively near the ending of stage 2. Stage 2 is further distinguished into two substages: 2a, which lasts approximately 9 years and 2b, which lasts approximately 6 years. The most prominent symptoms throughout stage 3, which remained an average of 13 years, were depressed ones. The third stage is divided into two phases, 3a, the decline of the hospitality symptoms and an increase in the depressive symptoms occur and in 3b, the positive symptoms completely disappear. The final stage starts 25 years after the first episode and is determined to be marked by mental dissonance. Fourth stage is sub-classified into 4a, which stays about 15 years and is marked by increase in the negative symptoms and substage 4b which lasts about 40 years and is predominantly occupied by the neurocognitive defects experienced by the patients (Fountoulakis et al. 2019).

12.3 Integrated Staging Model of Schizophrenia Spectrum Disorder

Even though the evaluated previous staging approaches for Schizophrenia Spectrum Disorders differ widely, they may be simply combined into a single cohesive model. Figure 12.1 illustrates this model and the stages it encompasses. To begin, all

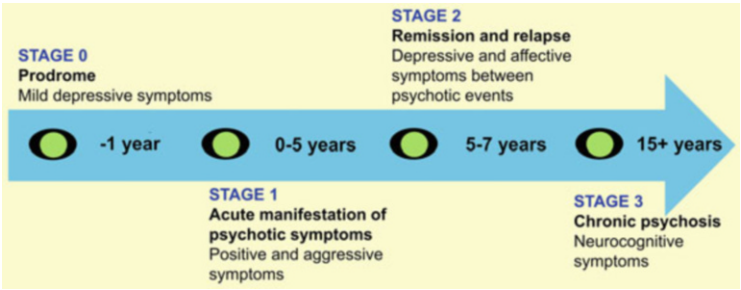

Fig. 12.1 The integrated staging model for schizophrenia spectrum disorder

conceptions include the initial psychotic episode. This early stage can be viewed as a turning point in the disorder, dividing it into a before and after period, and so might be considered initial stage of SSD. It is also the point at which the patient is in all likelihood of being diagnosed and managed for the very first time. As the prior phase, technically called the prodrome, is commonly established retrospectively and is strongly discussed from a therapeutic standpoint, majority, but not all, clinical staging ideas address it (Cosci and Fava 2013). Nonetheless, evidence for early treatments is increasing, and it may become increasingly significant in the future (Cornblatt et al. 2002).

In the same way, minor discrepancies are there in historical staging framework in regard to what events occur next following the start of psychotic manifestations. Few claim that there is just one phase following the onset of disease signs (Lieberman et al. 2001; Agius et al. 2010; Insel 2010), while others argue that there are three or many more separate stages (Hoffman 1982; Fountoulakis et al. 2019). Furthermore, the most dominant models propose (Singh et al. 2005; McGorry et al. 2010; Cosci and Fava 2013); two succeeding phases, a pre-chronic or residual stage marked by partial relapse, recurrence, and emotionally depressing signs, and a chronic phase marked by perpetual manifestations prevailing by cognitive and neurological abnormalities. In integrated staging system, these stages correspond to phase two (relapse and remission) and three (chronic psychosis).

12.3.1 Stage 0 (The Prodrome Phase)

Stage 0 is referred to as the prodrome in integrated staging model of SSD. It is stage when there are some subtle to moderate symptoms but no indication of full-fledged psychosis (McGorry et al. 2010). In terms of duration, the prodrome stage can stay from weeks to years, although it usually lasts around a year (Cornblatt et al. 2002). As prodrome just precedes the beginning of psychotic symptoms, it is a retroactive term that can only be noticed and characterized later (Cornblatt et al. 2002; Addington 2003). Symptoms exhibited during this phase are varied, with the majority being unpleasant symptoms such as depression, no motivation, and

goal-orientated behavior, as well as alterations in vision, attitude, mindset, and thinking (Addington 2003). In the course of prodromal phase, the patient's behavior changes significantly, and they may begin to feel cognitive disturbances, which can lead to worry or even hostility (Hoffman 1982). There are symptoms of aberrant dopamine production, prefrontal cortex (PFC) maladies, and gray matter volume decreases in various brain areas, in context of neurobiological alterations (Buehlmann et al. 2010).

Given the belief that the sooner therapy begins, the brighter the outcome for SSD, there is a lot of interest in commencing pharmacological therapies during the prodrome (Cornblatt et al. 2002; Addington 2003). The biggest issue with this idea, however, is the possibility of false positives, or people who, while experiencing symptoms and distress, may not acquire psychosis following the prodromal phase. As a result, many contend that providing antipsychotic medicine to these people is unethical, stating that even the most advanced antipsychotic drugs have adverse effects, can cause cognitive injury, and can permanently victimize the patient (Cornblatt et al. 2002; Addington 2003).

To address the issues of helping humans in the prodromal phase while avoiding false positives, researchers are working on developing factors which can appropriately assess patients who are in a "ultra-high risk" category (UHR) mental condition and thus are more inclined to manifest psychotic symptoms and advantage from therapeutic intervention (Addington 2003; McGuire et al. 2011). Personal Assessment and Crisis Evaluation (PACE) is one example of such criteria, which states somebody is at UHR of psychosis if they present with one or more of the following conditions: "(a) attenuated psychotic symptoms, (b) relatively short limited infrequent psychotic symptoms, (c) a marked decline in performance (held for at least a 30 days) with either schizoaffective disorder or a primary relative with psychotic disorder" (Cornblatt et al. 2002; McGuire et al. 2011).

The goals of intervention programs in the UHR group are multifaceted: first, to relieve the patient's symptoms; second, to lessen the chance of transition to psychosis; and finally, to shorten the period between the development of psychosis and the onset of antipsychotic medication (McGuire et al. 2011). More study is needed, however, to fully comprehend the dangers and benefits of pharmaceutical therapy throughout the UHR period. In the meantime, according to current guidelines, antipsychotic medication should only be used during the prodrome in most severe cases (Schmidt et al. 2015). With individual cognitive behavioral intervention, family psychoeducation, active ingredient utilize reduction, and neural protective elements like omega-3 fatty acids being the preferred interventions (Fountoulakis et al. 2019).

12.3.2 Stage 1 (Acute Manifestation of Psychotic Symptoms)

The acute presentation of psychotic symptoms, or the commencement of the maiden episode of psychosis, is the first phase of the SSD integrated staging model. Patients

in this stage of the condition are more likely to have positive symptoms such illusions, paranoid thoughts, or delusions, and to be in denial about the fact that anything is wrong and that they require medical attention (Hoffman 1982; McGorry et al. 2010). This denial frequently emerges as aggression or irritability, and the patient may be admitted to the hospital (Roberts et al. 2018). Symptoms like alogia, lack of motivation, and aggressiveness can be present besides dominant positive symptoms (Lieberman et al. 2001; Fountoulakis et al. 2019). Although there is currently no clear scientific proof on the cut-off period for the termination of the initial course, it is thought to be within first 5 years after the beginning of psychotic manifestations (McGlashan 1988). According to Fountoulakis et al., the initial phase of SSD stays average 3 years (Fountoulakis et al. 2019).

During the initial stage of SSD, the major aim of treatment is to alleviate psychotic symptoms and enhance the possibilities of patients reverting to their routine lives as quickly and successfully as possible. Antipsychotic drugs are used to do this (Wyatt 1991). Many patients, on the other hand, may require long-acting injectable drugs to enhance compliance (Johnson and Freeman 1973). Since multiple studies have shown that over 40% of patients are noncompliant in the initial 9 months of therapy as a result increasing their chance of recurrence (Miller 2008). Along with pharmaceutical therapy, psychologists, therapists, and social workers should provide additional assistance to patients and their attendants. In order to achieve better coping mechanism, the family may need to attend awareness or other counseling programs as well (McGorry et al. 2010).

Following the first incident, the illness can take number of different directions. In accordance with the Shepherd and team thumb rule, one-third of patients will go into remission and have no further episodes, the other third of patients will have one or more than one psychotic events (stage 2), and the third group will have several recurrences and unmitigated illness that will later be classified by chronic condition (stage 3) (Shepherd et al. 1989).

12.3.3 Stage 2 (Remission and Relapse)

The remission and relapse stage, which occurs between stages 1 and 3, is the most diverse phase of the illness. Patients have a transient or partial remission from the very first episode throughout the period of SSD, but subsequently, have a recurrence or even numerous recurrences of psychotic conditions in the form of bouts (McGorry et al. 2010).

Before remission, patient initially responds to therapy, which is generally measured through the specified degree of symptom relief (20–50%) on a standardized rating system, i.e., the Clinical Global Impression Scale or PANSS scale (Correll et al. 2011). The patient next progresses to remission, which is an "increasingly feasible phase in schizophrenia management, helping to increase the present ceiling of patient development beyond" stability, according to the RSWG (Remission in Schizophrenia Working Group). Although remission is characterized in a variety of

ways, it fundamentally refers to a time of the condition during which symptoms are moderate or there are no "active" psychotic episodes (Andreasen et al. 2005). Relapse occurs when symptoms begin to emerge after this minimal or free of symptom time and the patient's functionality deteriorates (Lee et al. 2020). However, as previously stated, a third of patients may not relapse but instead recover (Shepherd et al. 1989), a condition in which the patient is capable of functioning socially and occupationally while also experiencing significant symptom relief (Lee et al. 2020).

Fountoulakis et al state that the second phase lasts on average 9 years, followed by a 13-year period characterized by emotionally depressing symptoms (Fountoulakis et al. 2019). The second stage of SSD has a wide range of symptoms in terms of kind and severity. In most cases, however, negative and depressed predominate in between relapses, negatively impacting the life quality of patients (Novick et al. 2015). Positive and violent feelings may become more prominent after a relapse (Fountoulakis et al. 2019; Lee et al. 2020).

During this stage, the major therapeutic objective is to achieve complete remission, then avoid recurrence, and stabilize the patient with the help of expert care service (McGorry et al. 2010). Considering the greater prevalence of emotionally depressing symptoms, an important goal must be to reduce them, either through the use of distinct second-generation antipsychotic drugs like amisulpride or cariprazine, or through the use of a combination regimen of antipsychotic drugs as well as antidepressive medicine (Cerveri et al. 2019).

12.3.4 Stage 3 (Chronic Psychosis)

The Chronic Psychosis phase is the third stage of the integrated staging paradigm. Symptoms remain severe, persistent, or unremitting during this time of the SSD (Agius et al. 2010). Patients may have many relapses while primarily experiencing (depression-like/ anxious), and neural and cognitive manifestations, latter being the disorder's most dominant characteristic category throughout (Agius et al. 2010; Fountoulakis et al. 2019). In stage 3 of the disease, suicidal thoughts may also be more likely (Roy 1982). Patients, on the other hand, generally come to terms with their disease and learn to live with it (Hoffman 1982).

Stage 3 (Chronic Psychosis) begins around 15–20 years later the first occurrence. Patients who are in this stage of their illness are generally handicapped to some degree and are either jobless or retired (Costa et al. 2014; Fountoulakis et al. 2019). Treatment for chronic disorders is comparable to treatment for stage 2, with a focus on preventing additional illness aggravation and long-term stability, as well as augmentation methods and other behavioral therapies including active social involvement and/or rehabilitative programs (McGorry et al. 2010). Clozapine and other long-acting antipsychotic medicines are preferred pharmacological therapies (Agius et al. 2010); however, pharmaceuticals that target depressive and cognitive

issues (like cariprazine and amisulpride) may also prove to be beneficial (Cerveri et al. 2019).

12.4 Therapeutic Implications of Staging in Schizophrenia

Ailments created in a complicated manner are best portrayed in stages, and those stages will depict not just a specific point over the sickness yet additionally the fitting therapy for that stage. It tends to be vital in arranging the treatment of a complicated illness like schizophrenia. Schizophrenia has at least three stages. Treatment varies for all the different phases, and the normal result of the treatment will also be different in every one of the different phases of the sickness. Any endeavor to improve treatment in schizophrenia should consider the various phases of the disease, and target results should be suitable to these phases. Both pharmacological and mental interventions should be fitting to a specific phase of the illness. The utilization of therapeutic conventions that are unseemly to the phase of the sickness might prompt lesser quality results, and even iatrogenic mischief (Agius et al. 2010).

The essential point of clinical arranging is to increase the chances of recovery in the beginning phases of mental issues as well as forestalling movement to later stages (Dombi et al. 2021). The crucial intercessions in the prodrome period must be pointed toward regulating apoptosis and plasticity tweaking, to forestall or decrease the gamble of progress to full-blown disease. Some proof is rising out of Slovenian research that treating a patient in the prodrome phase with low-dose antipsychotic prescription and antidepressants or then again anxiolytics when fundamental might prompt better psychosocial results, lower clinic affirmation rates, and lower drug portions for support after the patients in all actuality do foster full psychosis. This proof should be contemplated and recreated but is consistent to the conviction that physiological shift can begin in prodrome phase, and not just at the start of the primary event. This proof proposes that treatment in the prodromal stage may further develop results (Agius et al. 2010). Pharmacotherapy is the pillar of schizophrenia management; however, some symptoms might persevere. Consequently, nonpharmacological ways, such as psychotherapy, are additionally significant. It is challenging to execute meaningful rehabilitation regimens for many individuals with schizophrenia without antipsychotic medications. The onset of drug treatment should occur no later than 5 years following the original acute event because that is when most of the changes in the human brain develop. For treating schizophrenia, the Texas Medication Algorithm Project has developed a six-stage pharmacological algorithm. First-line monotherapy including an SGA is stage one. If the patient has almost no response, he or she should proceed to stage 2, which entails monotherapy either with additional FGA or SGA. If yet no response, the person should progress to stage 3, which includes clozapine monotherapy and monitoring of the count of white platelet. Clozapine should be stopped if agranulocytosis develops. If stage 3 therapy fails to produce a response, patient should proceed to stage 4, which incorporates clozapine with SGA or FGA, or electroconvulsive therapy (ECT). If the patient

shows no reaction to treatment, stage 5 calls for monotherapy with an FGA or an SGA that has not been tried. Together, assuming stage 5 therapy is fruitless, stage 6 comprises mixed treatment with ECT, FGA, SGA, or potentially a state of mind stabilizer in the main course of psychosis, the point of treatment is the full reduction of side effects (Patel et al. 2014), and afterward the avoidance of backsliding during the basic time frame. The wanted down to earth result is return to full working, counting return to work and schooling, and this is accomplished by a mix of psychoeducation, atypical antipsychotics, avoidance of backslide by recognizing and treating of early advance notice indications, social mediations, mental treatment, as well as working with family (Agius et al. 2010).

As per current rules, the utilization of antipsychotic drug in prodrome stage is just suggested in more perplexing cases, when suggested mediations are family psychoeducation, individuals or gathering mental conduct treatment, dynamic substance use decrease, and neuroprotective specialists like omega 3. During stage 1 (the onset), antipsychotic meds are used, as oral antipsychotics due to being not so much invasive but rather more acknowledged over the long haul. Numerous patients, in any case, could require long-acting, injectable antipsychotics to increment consistence, as a few investigations showed that over 40% of the total of patients are unresponsive in the initial 9 months of medication, improving chances of relapse.

Stage 2 (remission and relapse), the essential treatment objective during this stage is first to accomplish total reduction and afterward to forestall backslide as well as to settle the patient interceded by expert consideration administrations. Given the elevated degree of negative and burdensome/nervousness like symptoms, the auxiliary point ought to be to lighten, either by utilizing an original second-generation antipsychotic drug, for example, amisulpride and cariprazine or a mix of antidepressant and antipsychotic prescription.

Stage 3: Therapy in the chronic disorder stage is like stage 2 treatment with a high accentuation on the avoidance of additional fuel of the ailment and long-haul adjustment close by with increase systems and other psychosocial treatments like active social cooperation as well as vocational rehabilitation. Favored pharmacological medicines incorporate clozapine and long-acting antipsychotic meds, even though medications tending to cognitive manifestations (for example, amisulpride and cariprazine) may likewise be of advantage.

Clinical arranging is a more refined type of analysis that gives data on how a sickness advances and where the patient exists in this movement. Considering the presumption, every phase may be portrayed by an ordinary clinical pattern with late phases being related with more prominent symptoms' seriousness and that addressing individuals in the beginning phases of the problem is highly proficient. The essential point of bringing clinical phasing into psychiatry field was to advance reduction and recuperation in the beginning phases of mental issues and thus to forestall patients to advance to later stages (Dombi et al. 2021).

12.5 Conclusion

To unite the abovementioned notions, an integrated schizophrenia spectrum disorder staging model has emerged, depicting the progression of SSD in four stages: prodrome (stage 0), onset (stage 1), remission and relapse (stage 2), and persistent psychosis (stage 3). The integrated model also gives a timeframe for when patients are expected to progress to the next stage, as well as which symptoms are prevalent and how to effectively treat them. To arrest the progression of the condition and bring comfort to the patients, every stage should be studied thoroughly and therapeutic approaches and regiments that cater to the demands of each stage independently must be developed. The requirement of the hour is a complete comprehension of each stage, as well as considerable study into each stage's various aspects. Various school thoughts regarding Schizophrenia are discussed in this study which help in timely diagnosis of suspected cases. Patients and their caregivers should be educated about the disorder, its progression, and treatment. This study will prove beneficial in creating awareness and establishing compliance to medicines for people from every sphere of life. Compliance to medicines will raise the quality of life in patients. This study also gives a timeline of disorder which will prove quite helpful for the people to assess severity of the disorder of schizophrenic people.

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Chapter 13
Stigmatizing Attitudes Toward Patients with Schizophrenia Among Medical Professionals and General Population

Bornali Mukherji

13.1 Introduction

Stigma can be defined as the condition that distinguishes a person in a negative way that leads to further hardship. According to Goffman (1963), stigma can be defined as any physical or social attribute or sign that so devalues an actor's social identity as to disqualify him or her from "full social acceptance".

Stigmatization against people with mental health problems is a form of social disapproval based on certain social factors, beliefs, behaviors, and personal characteristics that are contrary to the sociocultural norms. This can be viewed as signs of shame and disgrace that lead to one being cast away from the community.

Multiple studies in the USA and Europe have looked at negative beliefs held by individuals about people who suffer from schizophrenia. There is evidence from the literature on social and cultural history of medicine that in western European societies, stigma about this psychiatric disorder was very well established in ancient times and this was very common during the Medieval Period.

However, there is little work in nonwestern societies on stigmatization of patients who have been diagnosed with schizophrenia, reviewing the situation and discriminating against the mentally ill in societies where nonwestern medical practices dominate; in particular, Indian, Islamic, and Chinese medicine. It has already been found that psychological discrimination is common in India. Some problems are treated and discriminated against, while others are not. Also, in many societies there are supernatural, religious, moral, and magical methods of treating psychiatric disorders. This can further distort the perception of what schizophrenia actually presents as.

Discrimination against people with schizophrenia not only affects how these people seek help individually, but can also have a significant impact on policy

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formulation at the national level. Like India, many developing countries have serious problems with resources in the health care sector. There are a limited number of psychiatrists and mental health professionals. Most people who have schizophrenia or their family members seek help from faith healers and religious leaders. Culture itself has a complex, controversial, and sometimes confusing background. Current understandings of stigma involve a multilayered process:

Labeling: The everyday activity of creating categories and classifications is normal and is useful in modern life. However, labeling becomes stigma when the steps given below are involved.

Stereotyping: An association is perceived between the stigmatized individual and a stereotypical characteristic (for example, "schizophrenics are dangerous").

Separation: Placing the stereotyped individual into a different category from the rest of the people the sense of otherness or the concept of "us" and "them", results in false beliefs such as ("I am immune to having mental illnesses").

Emotional Reaction: The previous domains of labeling and separation are often accompanied by emotional reactions. This reaction is not limited to having anger, fear, or disgust, toward people who have schizophrenia but can also involve pity, feelings of guilt, or feeling responsible.

Discrimination: Discrimination takes place when stigmatization is acted upon by behaviors such as excluding, rejecting, or devaluating individuals who have mental illnesses. Discrimination can occur on a personal or societal level through various aspects of structural inequalities.

Power Differential: Discrimination has baneful and devastating consequences when the stigmatized person is in a vulnerable position because of a power differential related to socioeconomic reasons (for example, poverty and limited social capital), cultural affiliations (marginalized ethnic groups), or for psychological reasons (fragile self-esteem).

A population of 1.1 Billion people reside in India, out of which the prevalence of schizophrenia is approximately 3 in 1000 individuals. (Gururaj, et al, 2005). Suicide is a massive public health issue, with over 100,000 people dying by suicides every year (Patel et al. 2007a). Psychiatric disorders in India are not entirely experienced and understood in the same way as in Western countries (Saravanan et al. 2007) and the majority care is provided by the family itself. Many individuals with schizophrenia remain untreated, and those families who do seek treatment often turn to practitioners of Indian traditional medicine, religious healers, faith healers, and astrologers (Raguram et al. 2001). The unavailability of mental health practitioners, particularly in rural parts of India, places specialist psychiatric care out of the reach of most people (Thara et al. 2004).

The World Health Organization (WHO) advocates for the need to integrate mental health into public health care as the prime strategy for working toward addressing the global burden of the disease. In India, the National Mental Health Program also advocates for the integrative approach of mental health into public health care; however, there has been limited success in implementing this policy into

practice with only 24 of 600 districts in India currently being covered under this program (Patel et al. 2007b).

Promoting change in the Indian context is of utmost importance. While there are a wide range of potential frameworks with which one can consider such action, the most persuasive and empirical data exists for protesting stigma and discrimination as soon as they are encountered. Using awareness and education to counteract stigmatizing attitudes and discrimination toward people who have been diagnosed with schizophrenia, and endorsing interaction with people with lived experience with this psychiatric illness (Corrigan and Penn 1999).

We conducted this research to understand the stigmatizing attitudes prevailing among psychiatrists, nonpsychiatric doctors, and the general population. Information obtained may help design interventions to address the impact of these attitudes contributing to delays in seeking care, preventing timely diagnosis and treatment of schizophrenia, as well as serving as a barrier to recovery and rehabilitation. It ultimately reduces the chance of full participation in life. In India, there is a need to produce interventions that are based on scientific evidence that will address the negative attitudes toward people with schizophrenia and ensure the implementation of these interventions by involving users, caregivers, community health workers, and mental health service providers.

13.2 Methods

The total sample size consisted of 73 people out of which 20 participants were psychiatrists, 27 participants were nonpsychiatric doctors, and 26 participants belonged to the general community (belonging to any profession other than health services). The procedure of the data collection was done with the help of google forms. It is an online structured survey method. We collected data by uploading the questions in the same format as given in the questionnaire. The link to this compiled questionnaire (sociodemographic details and AQ-27) was then shared with the target population and responses were procured.

Participants who were chosen from the general community had a minimum of a bachelor's degree, belonged to upper socio-economic classes, with basic understanding of the English psychological terminologies. Only those participants from the general community were chosen who did not have a family history of schizophrenia. Psychiatric doctors who had a minimum qualification of MD in Psychiatry participated in the research. Data from those nonpsychiatric doctors were considered who had a minimum of 10+ years of experience in their respective specializations.

A sociodemographic questionnaire was administered which involved questions on age, gender, professional group, and information on previous personal and familial experience with schizophrenia.

The AQ-27 questionnaire that was designed to assess stigmatizing attitudes toward people with schizophrenia was administered and is based on nine stereotypical behaviors: responsibility (people with mental illness can control their symptoms

Items	Dimension
I would feel aggravated by Harry.	Anger
How angry would you feel at Harry?	
How irritated would you feel by Harry?	
I would feel unsafe around Harry.	Dangerousness
How dangerous would you feel Harry is?	
I would feel threatened by Harry.	
Harry would terrify me.	Fear
How scared of Harry would you feel?	
How frightened of Harry would you feel?	
If I were in charge of Harry's treatment, I would require him to take his medication.	Coercion
How much do you agree that Harry should be forced into treatment with his doctor even if he does not want to?	
If I were in charge of Harry's treatment, I would force him to live in a group home.	
I think Harry poses a risk to his neighbors unless he is hospitalized.	Segregation
I think it would be best for Harry's community of he were put away in a psychiatric hospital.	
How much do you think an asylum, where Harry can be kept away from his neighbors, is the best place for him?	
If I were an employer, I would interview Harry for a job.	Avoidance
I would share a car pool with Harry every day.	
If I were a landlord, I probably would rent an apartment to Harry.	
I would be willing to talk to Harry about his problems.	Help
How likely is it that you would help Harry?	
How certain would you feel that you would help Harry?	
I would feel pity for Harry.	Pity
How much sympathy would you feel for Harry?	
How much concern would you feel for Harry?	
I would think that it was Harry's own fault that he is in the present condition.	Responsibility
How controllable, do you think, is the cause of Harry's present condition?	
How responsible, do you think, is Harry for his present condition?	

Fig. 13.1 AQ-27 questionnaire items

and are responsible for having the illness), pity (people with mental illness are overtaken by their own disorder and therefore deserve concern and pity), anger (people with mental illness are blamed for having the illness and provoke wrath and rage), dangerousness (people with mental illness are not safe), fear (people with mental illness are dangerous), help (people with mental illness need assistance), coercion (people with mental illness have to participate in treatment management), segregation (people with mental illness are sent to institutions located far from the community), and avoidance (patients with mental illness do not live in society) (Corrigan et al. 2003). The AQ-27 starts with a brief description about a patient with schizophrenia, followed by 27 items that are scored on a 9-point Likert scale, where 1 means "no or nothing" and 9 means "very much or completely." Results for each construct are calculated by averaging the score of individual responses on each item. Questions in the avoidance domain are reverse scored. SPSS was used to calculate the ANOVA (Fig. 13.1).

The Following Brief Was Used in the Present Study "Harry is a 30-year-old single man with schizophrenia. Sometimes he hears voices and becomes upset. He lives alone in an apartment and works as a clerk at a large law firm. He has been hospitalized six times because of his illness."

13.3 Results

From the statistical analysis presented in Table 13.1 given below, key findings emerge about the overall stigmatizing attitudes and the nine domains of the AQ-27 test. The prevailing stigmatizing attitudes of the general population turned out to be the highest among our three sample groups, and the stigma in psychiatrists was the lowest.

The General Population's anger, fear, and the potentiality to segregate people with schizophrenia were the highest among all the three sample groups, and the levels in these same areas of fear, anger, and segregation, psychiatrists were seen to be the lowest (Table 13.1).

People from the general population were educated and knew what schizophrenia was but had never interacted with anybody diagnosed with the disorder; the increased levels of perceived dangerousness toward people with schizophrenia among the general population and lowest levels in psychiatrists (Table 13.1) can be explained through the *contact theory*.

The domain of coercion to seek treatment and take medication, the levels of avoidance, pity felt toward people with schizophrenia and viewing people who have schizophrenia to be responsible for causing their illness captured in our data were highly elevated in nonpsychiatric doctors. Lowered levels were seen in our general population sample (Table 13.1), followed by the psychiatrists.

In the domain of helping people diagnosed with schizophrenia, Psychiatrists believed that patients with this mental illness would need assistance in contrast

Table 13.1 Stigmatizing attitudes among psychiatrists, nonpsychiatric doctors, and general population

	Psychiatrists	Nonpsychiatric doctors	General population		
Items	Mean	Mean	Mean	*P*-value	*F*-value
Overall stigmatizing attitude	3.75	4.13	4.40	0.02	3.85
Anger	1.46	1.73	2.72	0.0002	9.48
Dangerousness	2.04	2.25	3.17	0.01	4.46
Fear	1.79	1.70	2.94	0.003	6.29
Coercion	5.51	6.88	6.39	0.01	4.25
Segregation	1.94	2.57	3.07	0.09	2.48
Avoidance	3.11	4.57	3.74	0.02	3.79
Help	8.43	7.55	7.97	0.09	2.48
Pity	5.79	6.46	6.26	0.41	0.89
Responsibility	2.74	3.41	3.39	0.18	1.73

The mean value, *P*-value, and *F*-value derived from our three sample groups depict the levels of overall stigmatizing attitudes and the nine stereotypical behaviors associated with people who have schizophrenia

with the nonpsychiatric doctors as they had the lowest levels of mean in this area (Table 13.1).

13.4 Discussion

The detrimental effects of stigmatization and discrimination on people with schizophrenia are well documented (Sartorius et al. 2010; Chatterjee et al. 2018) and include delays in seeking treatment, early treatment discontinuation, difficulty finding housing and employment, and adverse economic consequences (Sharac et al. 2010). Stigmatizing attitudes of society has been described as a "primary barrier" to treatment, recovery, and rehabilitation. Stigmatizing attitudes and discrimination are a well-documented barrier for people who have a lived experience of schizophrenia and are receiving adequate general medical care (Liggins and Hatcher 2005) and combined is one of the factors in reducing life expectancy. The life expectancy of people with schizophrenia is lower than the average population by about 15 years, and most deaths are due to heart diseases (both through increased risk factors and substandard preventive and curative treatment). Diagnostic overshadowing (process in which physical symptoms are misattributed to mental illness) has been described as a major contributing factor (Thornicroft et al. 2010). Family members of people with schizophrenia often report adverse effects on their own health and lives. Stigmatization and discrimination have serious economic consequences, not only for individuals and their families but also for society at large (Sharac et al. 2010). At the grassroots level, stigma and discrimination result in lower allocation of funding for mental health research, poorer and less organized clinical services compared to other areas in health care. Downgrading of those involved in these areas lead to barriers in recruitment into the field of psychiatry and other mental health care services.

While psychiatrists may believe that talking about neurobiology of psychiatry will help reduce stigma, the evidence suggests otherwise. Despite the growing endorsement of a neurobiological understanding of schizophrenia by the public over the past decade, there has been no decline in stigma (Martin et al. 2010). Focusing on biological factors as the cause of mental illness can reinforce the premise of people with schizophrenia as being unpredictable and as having a lack of control. Direct contact with people who have a lived experience of schizophrenia challenges the stereotypes. Direct communication has consistently been identified as the most effective means of producing sustained improvement in social attitudes (Thornicroft et al. 2010). Research suggests that focusing on recovery and perception, as well as opposing the feeling of "otherness" related to mental illness, is a very powerful strategy for human intervention (Clement et al. 2010).

Stigmatizing attitudes have always been seen as worrisome and essential but more recently attention has been focused on the reality of discrimination and the powerful negative effects that impact the people who have schizophrenia and the mental health care providers. There is an increasing consensus that we must move

past consideration of stigma alone to the foundational issue of discrimination against patients with psychiatric disorders, psychiatrists, and other mental health professionals and move forward to take social action through actively pursuing social inclusion.

Schizophrenia is highly disabling and costly for affected people, their families, and the community (Chatterjee et al. 2018). Mental disorders are increasingly considered to be a major contributing factor in the global health burden, including low-income countries and are often comorbid with infectious and noncommunicable diseases (Sartorius et al. 2010). Mental health remains at a low priority level in many low-income countries, and the unmet needs for mental health treatment are widespread (Goffman 1963). Up to 90% of people with mental illnesses in low- and middle-income countries barely receive even basic mental health care (Scambler 1998). This neglect continues despite having conclusive evidence that low-cost treatment (drugs, psychotherapy, psychological treatments, and social rehabilitation) is possible, affordable, and cost-effective for many mental disorders, and can be successfully delivered to primary health care facilities (Liggins and Hatcher 2005).

Education and Awareness The first primary step in addressing the problem of stigma and discrimination is to make them visible, both to the mental health care providers and patients and to the community at large. There are no formal curricula in place that addresses stigmatization and discrimination in the clinical training of mental health care providers. These issues may be difficult to pinpoint, both in others and in oneself. Quite a number of us are unable to act or respond when we witness stigmatizing or discriminatory behaviors toward people who have been diagnosed with a mental illness like schizophrenia because of our own internalized stigma and a lack of knowledge and experience to guide us as to how we can reprimand this behavior in a respectful and appropriate manner.

Provide Leadership in Working with Medical Students Medical schools have traditionally been described as a seedbed for stigmatizing and discriminatory behavior toward people with mental illness and their caregivers (Thornicroft et al. 2010). It is potentially an essential venue for directly addressing and counteracting the stigma and discrimination and for providing experiences for medical students who will inform their future professional lives and work with patients. Conventional teachings on a mental illness like schizophrenia and mental health alone have not helped reduce stigmatizing attitudes and behaviors. Exposure of the medical students to people who have recovered and have been rehabilitated from schizophrenia through virtual or physical lectures, interactive seminars, and role plays appears to be a potent experience that changes medical students' attitudes (Coodin and Chisholm 2001). The power of direct interaction with people with this psychiatric illness who have recovered, challenges the negative stereotypes.

Incorporation of Stigmatization, Discrimination, and Social Inclusion in MD Psychiatry Curricula Explicit education should be given about stigmatizing attitudes and discriminatory behaviors and they must be included in MD psychiatric training as well as education about how it can be combatted (Sartorius et al. 2010).

Being Appropriate Role Models for Mental Health Trainees Psychiatry professors have a particular responsibility as role models for people who train under them. In addition to dealing with their own attitudes and behaviors, they must directly label stigma and discrimination wherever it appears and are supposed to reconsider and process the incidents along with the trainees. Role modeling directly in addressing stigmatization and discrimination at the right moment has great potential in changing attitudes among trainees.

Recognize Our Problems and Change Our Behavior Psychiatrists and other medical practitioners are also not immune to the stigma and discrimination toward people with schizophrenia. This is understandable given the fact that psychiatrists are members of the society where such ideas are widespread, pervasive, and exist in our society from earliest socialization and that our medical training is riddled with such prejudices. Psychiatrists may carry more negative beliefs than the general public (Schulze 2007) and have more pessimistic ideas about prognosis and recovery, perhaps due to often dealing with patients who have schizophrenia that are difficult and are at the treatment resistant end of the spectrum (Thornicroft et al. 2010). According to Myers, "Overcoming stigma in ourselves is a lifelong challenge" (Myers 2001). A large minority of patients having schizophrenia and their families have described psychiatric treatment as dehumanizing and that they feel devalued in their encounters with psychiatrists (Thornicroft 2006). We must be aware of these experiences to ensure that we provide humane and professional care.

Labeling Stigma and Discrimination When We See It We need to label stigmatizing behaviors and discrimination when we see it and make it socially unacceptable to do so against people with any psychiatric illness. It is important that we speak of the many injustices we see in everyday life. Each and every one of these occurrences is an opportunity to address the stigmatizing attitudes and discrimination and can be of utmost importance in making offenders reflect upon their behavior or change their behavior. It is important that we challenge the discriminatory portrayals of people with a mental disorder whenever we meet them.

Include Discussions of Stigmatization, Discrimination, and Social Involvement in Our Clinic and Patient and Family Work Mental health professionals need to promote and encourage discussions on stigma, discrimination, and social exclusion in our work with psychiatric patients and families. These problems are central to their lives and appropriate topics for discussion and targets for intervention. Self-Stigmatization and discrimination are commonly experienced by people with schizophrenia (Brohan et al. 2011). Clinicians need to focus on making this self-stigmatization known and work through it. It is essential to focus on the strengths of the patient along with their illness or symptoms and set an agenda to promote mental health as well as ameliorate psychopathology in our clinical practice. Excellent mental health care goes beyond the simple focus of psychopathology to the development of mental health and well-being. It is crucial to communicate with patients and their families about divulging their psychiatric history, including who they want to disclose the information to and what they expect from their disclosure. The

discussion of when and how they disclose is an important and often overlooked part of clinical care.

Bridging the Difference Between "Us" and "Them" In society, discriminatory behavior becomes psychologically acceptable when one is denied the essential human features of a person by being classified as "other" or "them" as different from us. In addition, inequalities in power can prevent a stigmatized individual from regaining his or her human status, promoting further discrimination. Recognizing our common identities, bridging this perceptual gap, does a lot to reduce stigma and discrimination.

Develop and Teach Direct Communication with Patients Bridging the us and them gap with patients occurs when a patient who has been diagnosed with schizophrenia is met not only in medical settings but also in a broader range of situations, thus showing that he or she is not just another case, but a fully functioning human. Direct contact with a person is considered an important factor in the fight against stigma and discrimination (Thornicroft et al. 2010). This can be incorporated into mental health training as a preventive measure (for example, by arranging nonclinical meetings between trainees and patients).

Listening to Patients Giving the patients a central space to what they have to say—in their words—is important. Doing so can effectively combat psychological ignorance to the humanity of the other person, empower patients, and promote co-operative, less paternalistic relationships in line with new approaches to psychiatry (Bracken and Thomas 2006). Patients can be involved in diagnostic and therapeutic processes, research, participation in paradigms, and in the work of clinical and inpatient care providers by giving user inputs in the designing of treatment and treatment structures.

Use the Media to Address Stigmatization and Discrimination The media plays a key role in perpetuating and combating stigma and discrimination. The negative media beliefs toward people with schizophrenia, their families, and mental health professionals are common and are among the most damaging to people. Such disclosures should be protested. Recent research comparing the advertizing of psychiatric and nonpsychiatric medications has shown significant differences that perpetuate stigma (Foster 2010). Organized mental health care needs to monitor the media and address stigma when it is identified. Working directly with the media to provide up-to-date information through local and national experts on media communication and communication skills. Guidance on responsible reporting on mental health disorders like schizophrenia should be provided.

Promote Social Inclusion The social exclusion of patients with schizophrenia is evident in unemployment, lack of communication, reduced social roles, and a lack of economic and social participation. Because poverty, disability, and the lack of social networks are strongly linked to stigmatization and schizophrenia (Gaind 2010), it is our moral and pragmatic principle to actively promote social inclusion (Sayce 2001; Berry et al. 2010). A deep cultural and social shift is required to achieve inclusion of

patients who have this psychiatric illness; both hefty educational efforts for mental health care providers and patient involvement in this process are considered necessary steps in such a setting.

Focus on Recovery and Quality of Life The recovery movement is an effective modern example of initiating patient involvement in the clinical setting. Contemporary usage of the word recovery designates the processes by which people with lived experience with various mental illnesses participate, work, learn, and live fully in their social settings (Whitley and Drake 2010). A recovery orientation includes an emphasis on empowerment of the individual to assume as much responsibility as possible for their recovery and a focus on instilling hope, optimism, and a satisfying and meaningful life where the individual contributes to the society (Deegan 1996). Recovery can take place in the face of ongoing symptoms of illness, despite them, the individual can acquire the skills to learn to cope, adapt, and thrive (Anthony 1993). The mental health professional's role is to encourage recovery through individualized, person-centered care, the use of a strengths-rather than a weakness or deficit-based model, empowering patients, and endorsing decision making that is self-directed and shared. Instilling hope is an extremely underrated yet important component.

According to the results of the research we conducted, we found no significant differences in the means of four sub-domains of stigmatizing attitudes toward people with schizophrenia among psychiatrists, nonpsychiatric doctors, and the general population. These included *segregation, help, pity, and responsibility*. However, it is evident through the data provided in Table 13.1 that the individuals falling in the general population group had increased levels of stigma compared to psychiatrists and nonpsychiatric doctors. It is essential to note here that only those individuals were included in the general population sample who did not have any contact with a person having a psychiatric disorder. But they all belonged to upper socio-economic backgrounds who were literate and understood the basic psychological terminologies and their meanings.

There were significant differences (with a 95% level of confidence) in the means of three subdomains of stigmatizing attitudes toward people with schizophrenia among psychiatrists, nonpsychiatric doctors, and the general population. These included *dangerousness, coercion, and avoidance*. The trend in the data suggests that individuals from the general population felt significantly increased levels of dangerousness toward people with this mental illness. However, significantly increased levels of coercion and avoidance toward people diagnosed with schizophrenia were seen among nonpsychiatric doctors. This may be an important aspect in understanding why people with psychiatric disorders and their family members feel dehumanized by the experience of disclosing their mental health condition to even health care workers.

There were significant differences (with a 99% level of confidence) in the means of two subdomains of stigmatizing attitudes toward people who have schizophrenia among psychiatrists, nonpsychiatric doctors, and the general population. These included *fear and anger*. The trend seen in our data suggests that individuals from

the general population feel significantly increased levels of fear and anger toward people with schizophrenia. Since there is a lot of perceived uncertainty and lack of control associated with persons having this disorder, individuals who have never had direct contact feel higher levels of fear and anger toward them. It not only creates a barrier for people with schizophrenia to access health care, but they are also isolated from the same society that is supposed to be an essential component in efficient rehabilitation.

The nine subdomains mentioned above together form overall stigmatizing attitudes. There were significant differences (with a 95% level of confidence) in the means of stigmatizing attitudes toward people having schizophrenia among psychiatrists, nonpsychiatric doctors, and the general population. Although there were significantly high levels of stigmatizing attitudes among individuals who belonged to the general population, one cannot ignore the finding that even though mild, there were noticeable stigmatizing attitudes seen in mental health professionals themselves. It only shows that Psychiatrists, too, are a part of the same society and are not immune to stigma even if they treat and interact (in clinical settings) with people who have this psychiatric condition and still hold stereotypical views toward them.

13.5 Conclusion and Implication

In conclusion, the General Population who know the basic psychological terminologies and have the understanding of them still show significantly higher levels of stigmatizing attitudes. They are not aware of the actual presentation of schizophrenia, and have never seen or interacted personally with people with this psychiatric disorder. This indeed leads to the fear of the unknown.

A trend can be seen with nonpsychiatric doctors who understand the biomedical model of schizophrenia but have not been exposed enough to people who not only have been diagnosed with schizophrenia but have also recovered. This results in the facilitation of higher levels of coercion into treatment and avoidance seen among nonpsychiatric doctors. It is essential to look at the spectrum of people who have recovered, are in remission and have been rehabilitated as fully functioning individuals of the society, and are contributing to their community and supporting their own families.

It is easy to say that understanding the biomedical model of schizophrenia can reduce stigmatizing attitudes but in spite of that understanding, psychiatrists' and nonpsychiatric doctors' stigma cannot be completely eradicated. For a country like India where astrology, magical and supernatural beliefs, and treatment by Ojhas are rampant and dominant, we need to make implementations at the grassroots level and include mental health care in the primary health care settings in all the districts of the country.

We need to label stigmatizing behaviors and discrimination when we see it and make it socially unacceptable to do so against people with schizophrenia or any other mental illness. It is important that we speak of the many injustices we see in

everyday life. Each of these incidents is an opportunity to address stigma and discrimination and can be instrumental in making offenders reflect upon their behavior or change it. It is essential that we challenge the discriminatory portrayals of people with a mental disorder whenever we see it occurring. Recognizing our common identities, bridging this perceptual gap, does a lot to reduce stigma and discrimination.

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Chapter 14
Rehabilitation of Schizophrenia: Practical Interventions

Pratibha Swami

14.1 Introduction

Schizophrenia or schizophrenia spectrum disorders are serious debilitating mental conditions in which delusions, hallucinations and unpleasant symptoms are common psychotic indicators. Loss of contact with reality, altered sensory processes, disorganized thinking and, in many cases, social and vocational decline are also symptoms. The social and occupational decline remains an etiological and therapeutic challenge for the family as well as for the therapist. Apart from positive, negative and disorganized symptoms, cognitive impairment is now recognized as further clinical features of the disorder (Chatterjee et al. 2018). Some theories suggest neurotransmitter imbalance (Bansal and Chatterjee 2021), few debates on brain structure change (Ray and Sovani 2018), and some suggest carrying childhood trauma and transition from adolescent to adult. From genetic to environmental, whatever the cause is, the symptoms remain problematic for the person and affect the family of the person with schizophrenia. According to various studies cited by Graham Thorndike, the prevalence of schizophrenia is more than 1% of the population, so a large no of people are affected. This disorder is debilitating as almost all people with schizophrenia show cognitive deficits in various domains, including thinking, perceiving, executive functioning, working memory, episodic memory and emotional expression (Chatterjee et al. 2019). The social outcome includes reduced rates of employment and financial independence. If we analyse the occurrence of symptoms, they begin early in life, in adolescence or young adulthood (Tandon et al. 2009). A nonspecific impairment with cognition, motor and social functioning can be noted during this phase, which is referred to as the premorbid phase. It is accompanied by poor academic achievement too; the intervention at this stage will give best management skills and help the person to perform well in future life, but most of the time

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the diagnosis becomes difficult as the symptoms are overlapping with other mental disorders, the next phase is a prodromal period characterized by Initial positive signs which are followed by decline in function. This phase can last for few months to few years, and the mean duration can be of 5 years. The next phase is the psychotic phase. In this phase, repeated psychotic positive symptoms are prominent, and after few years, this phase is followed by stable phase where few positive and more negative symptoms are observed (Foussian and Remington 2010), the significant cognitive and social deficit is seen in the stable phase (Tandon et al. 2009), and rehabilitation is critical at this stage.

14.2 Rehabilitation of Schizophrenia

Rehabilitation is the approach which helps the individual with schizophrenia in restoring and managing In individuals with schizophrenia, along with cognitive deficits and management of social skills and restoration or management of vocational skills, the rehabilitation approaches are not very traditional in individuals with schizophrenia, as before the 1960s, individuals were either placed in mental asylums/hospitals or kept untreated. Even in the mental hospitals, no real treatment approach was recognized; individuals were controlled by medicine and other physical approaches. If we talk about the history of treatment given to individuals with schizophrenia and other psychotic disorders, a tranquilizing chair was designed by Dr Benjamin Rush, with the belief that madness/psychosis is an arterial disease that results in inflammation of the brain. In this method, the patient was allowed to sit on the chair with covered eyes, steady arms, and was bound by leather strips. Here the chair was supposed to control the blood flow towards brain and help in controlling or reducing the muscular movements. It was believed that this was the appropriate treatment of insane (Franklin et al. 1948), but in reality it neither do any effect of the schizophrenia.

Moral treatment was a more humanistic approach to the treatment of people with chronic and severe mental illness. We believe in creating a calming and relaxing environment for the patients with therapies like fresh air treatment and hydrotherapy. In fresh air treatment, the in-house patients in the institution were introduced to a structured daily routine to support and nurture their mental health and healing, they were allowed to practice exercise, and psychoeducation about their health was provided in the natural environment and surprisingly it showed positive results on the mental condition of the patients. Another non-medical approach was hydrotherapy which involved the bathtubs with different temperature, the water can be cold, warm or can be hot according to the condition of the patient and need of the therapy, the treating doctors of these wards would carefully instruct the staff to create just the right temperature for the patients, the patients would lie in the bathtub, sometimes sit for many hours, this would be used to an agitated patient. Apart from these few invasive techniques like fever cure and frontal lobotomy were also performed on individuals with schizophrenia (Kelly and Mitchell-Heggs 1973); at that time,

knowledge was very limited and treatment was in the trial phases, although few people got benefitted by these approaches, but it also violates the human rights of the individual as the treatment decisions were purely taken by the doctors on the medical abnormality ground. The psychiatric grounds were ignored, but with time treatments were modified with non-invasive and more humanistic approaches, to make the individual with schizophrenia a part of their own community. Two major approaches of rehabilitation were introduced simultaneously, the medical rehabilitation and community-based rehabilitation (Harrison et al. 2001). The Medical rehabilitation approach focuses on the imbalance of neurotransmitter and neuroreceptors and the chemical drug interventions to manage the symptoms and psychotic episodes of schizophrenia. The Community-based rehabilitation focuses on restoring and managing the lost abilities of person with schizophrenia and integration of the individual within their own community.

14.3 Community-Based Rehabilitation

Community-Based Rehabilitation is a community development technique aimed at improving the lives of people with disabilities (PWDs) in their own communities. WHO pioneered community-based rehabilitation (CBR) when we talk about schizophrenia. People with schizophrenia will benefit from CBR since it will assist them achieve their fundamental needs while also ensuring their involvement and participation. CBR is implemented by persons with disabilities, their families and their communities working together (IHME 2019).

Community-Based Rehabilitation is a community development method aimed at rehabilitating, equalizing opportunities, and socially integrating all people with disabilities. It focuses not only on the medical rehabilitation but also in the psychosocial development of the person. In the CBR approach, the care and services are not delivered or determined by the needs of an institution or group of professional; it is not segregated from the services of the other people. Instead CBR involves partnership with disabled people, adult and children, their families and caregivers. It involves capacity building or increasing functional capabilities of people with schizophrenia and their families, in context to their family and culture. It is a holistic approach encompassing physical, social, employment, educational, economic and other needs. It promotes the social inclusion of people in existing mainstream services (WHO 2009).

14.3.1 Why CBR Is Required

CBR is a strategy to enhance the living and working conditions for people with disability, and when we talk about schizophrenia, it causes psychosis which contributes in social isolations and considerable disability which have an impact on

every aspect of life, including personal, family, social, educational and vocational functioning. People with schizophrenia are frequently subjected to stigma, discrimination and violations of their human rights (Zipursky 2014). It is also reported by WHO in an article on factsheet on schizophrenia in January 2022 that two out of three psychotic patients do not receive the specialized mental treatment in any home or institutional setting, although as per various studies, there are a variety of effective treatment options for persons with schizophrenia, and at least one out of every three people with schizophrenia will be able to recover completely.

14.3.2 Goals of Rehabilitation

The main goal of rehabilitation is to restore the abilities of the person with schizophrenia, so that he/she can achieve the target of self-care, and other social and financial independence, for which few practical strategies should be applied (Habibi et al. 2015), as integration of medical treatment with psychosocial interventions will help the persons achieve the goals within their limits, and it will help in boosting confidence and dignity in the person itself. Practically every person is different and every person has different needs, and the rehabilitation goals are also decided according to the severity of the condition and other needs/characteristics of the particular person.

Few of the goals are: first, Creating and Advocating Awareness about the rights of disabled people and how they can be converted from tax user to tax payer if providing proper guidance and trainings; the second goal of CBR is Pre-Vocational Training, in which the assistance is given at school and college level to develop the required skill according to the interest of the child, or give priority to the social skills and abilities and develop the skill (Saperstein and Kurtz 2013); another goal of CBR is Vocational Training, intensive training programs are planned for the improvement of skill and to enhance their employment or self-employment opportunities. Other goal is to provide the scope for self-employment by promoting the government policies designed for people with disability, but the main goal of CBR is to make the person a part of society (Tauber et al. 2000), in CBR they believe that each individual with any mental or physical disability has right to enjoy his/her given life, like others and no discrimination towards them is appreciated in the society. No individual should be left behind and should be provided with opportunities within the society (Moriana et al. 2006) so integration within the society and mainstreaming the people with disability is the major goal of CBR. The community-based rehabilitation will work on five major principles: **Equality**, **Social justice**, **Solidarity**, **Integration** and **Dignity**.

14.4 Need of CBR for Person with Schizophrenia

According to Civil Rights of the person with disability and mental health act, every person has right to live independent life including the people with mental illness, and everyone should meet their basic needs to make them empowered to understand and utilize their rights the CBR is needed and provide integration within the society.

1. **Family life**: As a disabled person, you should be able to find a partner, have children and have your own family. You should be able to live with your family and be a part of your community.
2. **Food and Shelter:** Everyone including special population has right to get food and shelter, they should be able to move freely at home and in the surroundings without interruptions.
3. **Education and Schooling:** As a child with special needs, they should attend school and share their education with other non-disabled children, and they should be given equal educational and training opportunities so that they can prepare for job and independent lives.
4. They should be free to join any social or public group to enjoy their leisure time.
5. **Public services and political participation:** They should have access to all public buildings and public transports, they should be allowed to roam around public places, they should not be denied membership of any association and organization, as well as the right to vote and participate in government and non-government sectors, their voice should be heard, and all the services should be provided to them.

14.5 Domains of CBR

The community-based rehabilitation has five domains, and the five domains have five sub domains. The five domains are medical rehabilitation, educational rehabilitation, social rehabilitation, livelihood or vocational rehabilitation and empowerment. Every person with mental disability is eligible to get help in specific or all the domains of CBR. Now we understood the importance of CBR and why it is important for the person of schizophrenia to get rehabilitation services. Now we can understand the practical application of CBR in real-life scenario. CBR programs are formulated to actively involve the community in the entire rehabilitation process. The important parameters of CBR are medical rehabilitation, education, social integration, vocational rehabilitation. The following steps are required to implement the CBR strategies:

- Identification of the person with schizophrenia
- Providing need-based services, psychosocial, social, and vocational
- Promoting integrated psycho education
- Providing special assistance to the identified children in college/school
- Creating awareness among the public about the illness and its prognosis

- Conducting awareness program in the rural areas
- Providing counselling and guidance to caregivers of schizophrenia
- Building networking with other NGO/support bodies
- Providing economical rehabilitation, through training in different small trades
- Facilitating them with career and vocational counselling, for self-awareness
- Enhancing the knowledge of people with disabilities to avail various government and non-government scholarships/pensions/and other benefits if any
- And with this providing advocacy and support for people with mental disabilities

In CBR programs, therapists enquire about the needs of the individual and provide information about the illness and its prognosis, they talked about social model and how it can be implemented, they help people with schizophrenia in decision-making for community-based rehabilitation programs, they also provide information about the services that exist in their community, and they also link people with mental illness with self-help groups.

14.6 Management and Support

Medication, psychoeducation, family interventions, CBT and psychosocial rehabilitation are among the successful treatment choices for patients with schizophrenia, which help in activities of daily life, facilitate assistive living and support employability for people with mental illness. For persons with schizophrenia, as well as their family and/or caregivers, a recovery-oriented approach—providing people agency in treatment decisions—is critical.

14.7 Review of Literature

Need of the Study Schizophrenia is the disorder which not only affect the patient but also will equally affect the family and caregivers. The medical rehabilitation can help in managing and reducing the positive symptoms only (Deegan 1988), but to take care of social and cognitive well-being, community-based rehabilitation is necessary, which not only helps in the field of cognition but also helps the person with schizophrenia to manage well and integrate well with the society and within the society. It will help in providing rehabilitation in educational field, occupational field and social recognition too. CBR also helps in empowerment of the people with schizophrenia by providing proper counselling about their rights in the society.

Currently, the vast majority of persons with schizophrenia do not receive mental health treatment anywhere in the globe. Approximately 50% of people who are diagnosed with schizophrenia go to mental hospitals and only 31.3% receive special mental care (Jaeschke et al. 2021). It is a known fact that mental hospitals alone are not able to provide complete care for people with schizophrenia. Most of the

resources of mental hospital are not effectively used in the treatment process, and in this course of treatment, they sometimes violate the basic rights of people with mental illness. So the need of elaborating the care methodologies from mental hospitals to community-based services is accelerated (Jääskeläinen et al. 2013). Such efforts start with the range of quality community-based services. Integrating mental health into primary care and general hospital care is two possibilities for community-based mental health. Community health clinics, day centres, assisted housing, and home-based support programmes are all available. It is critical that individuals with schizophrenia, family members, and the larger community participate in giving support (Bowie et al. 2006).

Community-based rehabilitation is indicated as important and appropriate intervention for patients with schizophrenia especially for the lower income group, according to the WHO Mental Health Gap Program done in Ethiopia. In addition, these environments have the ability to bring together mental health practitioners. People with schizophrenia in the intermediate income category may benefit from community-based therapies as well. Ten participants living in sub-district area were recruited for baseline prime cohort study as a part of the Rehabilitation Intervention for People with Schizophrenia in Ethiopia (RISE) project. It is a 1-year study of implementation of CBR intervention for people with schizophrenia in Rural Ethiopia conducted in 2014–2015. CBR was given to all participants in addition to the other prime interventions at the health centre, and it was given over a period of 12 months. Process data was collected continuously over the course of a year to answer questions about the acceptability and practicality of CBR, while qualitative data was collected at 6 and 12 months to address research questions about CBR's potential consequences. They also introduce the concept of change theory.

"A strategy describes how a program brings about certain long-term results through a logical sequence of intermediate outcomes" according to theory of change. Figure 14.1 is a map of the RISE theory of change created during the intervention development phase. The long-term result was "sustained enhanced functioning" (yellow box). Intermediate program outcomes and unintentional pathways are for better functioning. Thirteen assumptions were found (represented in orange colour), which describe what needed to be in place to move forward from the intermediate outcome to the final outcome. The purpose of the study was to test assumptions that were grouped into the three research questions. This pilot study yielded a wealth of information about acceptance. The study concluded the acceptance of feasibility of community-based rehabilitation alternative to schizophrenia patients are cared for in a facility in Ethiopia over the course of a year. It suggested that the incorporation of several sources of qualitative data to enhance the trustworthiness of the conclusions was a positive, and it concluded that community-based rehabilitation may be an acceptable and feasible alternative to facility-based care for people with schizophrenia. CBR may be able to improve functioning by assisting with livelihoods, enhancing family and community support, improving access to antipsychotic medicine, and boosting hope. Contextual variables, such as poverty and a lack of antipsychotic medicine, are, however, significant obstacles.

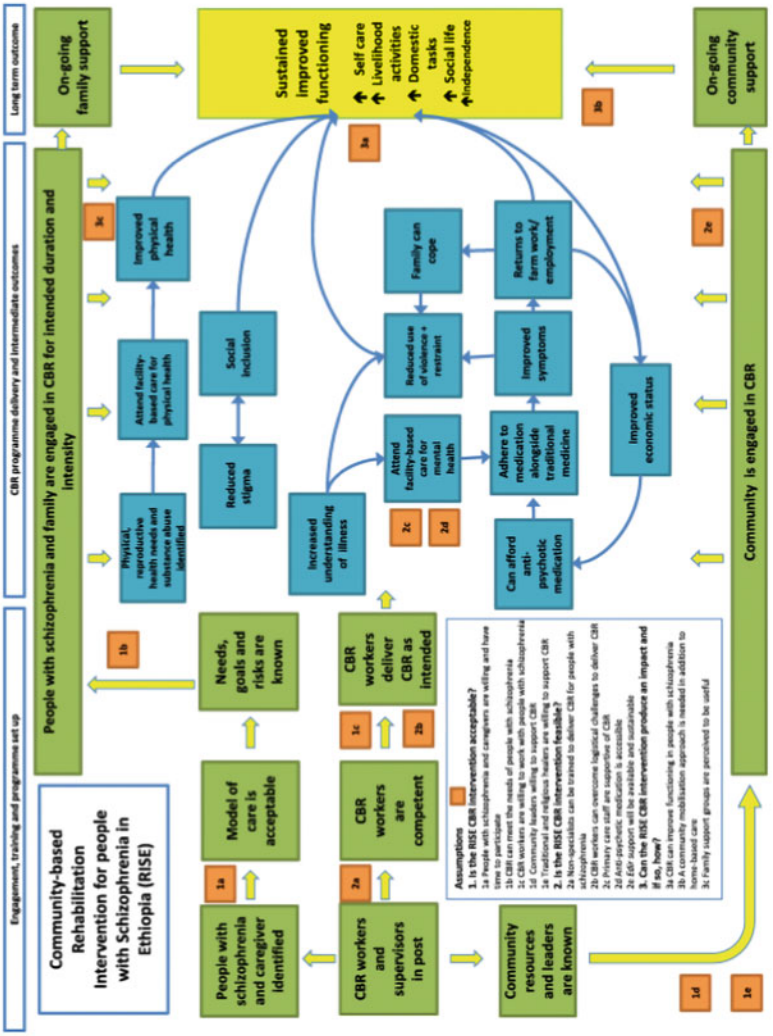

Fig. 14.1 Theory of change: CBR intervention for people with schizophrenia in Ethiopia (RISE): a 12-month mixed method pilot study

Another piece of online research addressing the effectiveness, essential elements and modifiers of response to cognitive remediation for schizophrenia was published in ***JAMA Psychiatry***, Randomized Clinical Trials, A Systematic Review and Meta-Analysis. The most complete meta-analyses incorporated the findings of 40 research and revealed effect sizes (ES) on cognitive and functional measures that ranged from low to moderate. Many new trials evaluating various CR programmes have since been published, and more than 20 meta-analyses have focused on specific subjects, such as efficacy in patients with recent onset schizophrenia, in patient setting, or negative symptoms, or of a specific form of intervention. The suggested report items for systemic review guidelines were used to conduct a systematic review and meta-analyses. There were 130 research studies that covered populations with representative of patients with schizophrenia, using mental health services, at various phases of illness and clinical conditions, reporting 146 control cognitive remediation with 8851 individuals, including two continuing investigations. The average length of treatment was 15 weeks. This meta-analysis is the most recent and thorough assessment of cognitive remediation effects in schizophrenia patients. It drew on more than 8000 participants and a vast number of research to find an overall positive influence of cognitive remediation on global cognition and functioning. This verify the previously stated effectiveness of CR.

Ian Falloon and his colleagues created the "Optimal Treatment Project" to see if the evidence-based biological and psychosocial treatments are better than routine clinical management of schizophrenia. Social skills training is one of the evidence-based techniques. Through rigorous coaching and trainings of therapist and other practitioners, assertive community therapy, antipsychotic medication with compliance training and family psycho-education were integrated in routine clinical practice. Despite the fact that no attempt was made to separate the relative advantages of each of these modalities, the program was tested in a controlled trial in Turkey, where it was compared with the given treatment at the same mental clinic. A total of 100 individuals with schizophrenia disease who had not been diagnosed for more than 10 years were randomly assigned to one of two therapy groups. All groups of patients were treated every 2 weeks for the first 3 months, then once a month for the next 2 years. The psychotic symptoms, overall symptoms, disability, quality of life and family stress are all factors to consider. Individuals in the best treatment program showed significantly more improvement. The comparison group's monitoring and excellent standards of care resulted in a low rate of hospitalizations. After a 6-month period of treatment, the patients who received conventional care continued to meet their personal goals, manage their stress and maintain their resilience. More than 1000 patients from six nations participated in the trial, with significant gains in social adjustment, quality of life, self-esteem and re-hospitalization.

In another study, 547 young patients after the first episode of psychotic illness in Aarhus and Copenhagen study, in Denmark, were randomly assigned to the integrated and comprehensive treatment programmes or the standard treatment available in cities. The comprehensive programme included services like assertive community treatment, social skills training, and multidisciplinary treatment. Social skills training, which focused on medication self-management, conversational skills, and

coping with symptoms and taught coping and problem-solving abilities using behavioural principles, resulted in less co-morbid substance misuse and much higher treatment satisfaction. It also demonstrated that after skill training and family counselling, negative symptoms improved significantly.

Another review of Electronic database (PubMed, Science Direct and Google Scholar) was searched for research on the effects of cognitive remediation, psychoeducation and CBT that were published in English between 1995 and 2017. The following terms are searched for screening ("Schizophrenia") and ("cognitive remediation" or "psychoeducation" or "family psychoeducation" or "social skills training" OR "cognitive behavior therapy"). The results show the impact of psychosocial intervention, and the functional outcome seems to be improved by combining the elements from each therapeutic approach. The CBT and psychoeducation allow patients to gain knowledge about their illness and play an active role in recovery. While social skill training and cognitive remediation may improve adaptive skills, more study is needed to uncover the synergistic benefits of combination interventions as well as the active component of effective therapy methods.

People with schizophrenia ($n = 1200–1400$) in psychoeducation programs for schizophrenia reported a significant increase in treatment compliance and a reduction in readmission and relapse rated in the short term of 6 months, compared to those who received only standard psychiatric care, according to a systemic review of 44 randomized controlled trials published between 1998 and 2009. This is also observed that when psychoeducation is provided for long term 6–8 months, this promotes improvement in social and global functioning. The satisfaction of mental health treatment in patient and family is also increased when psychoeducation was provided with other treatments. Initially there was no significant difference in the primary outcome of relapse, or mental status between the psychoeducation and standard psychiatric care. This review was conducted in the hospital, whereas most people of schizophrenia were taken care in the community. But in long term psychoeducation showed significant improvement in the treatment compliance.

Beck and Rector present theoretical underpinnings for the use of CBT for schizophrenia in their review. They explain a premorbid neurocognitive deficit that makes an individual prone to adverse experiences (such as failure in school) and leads to dysfunctional beliefs, like I am inferior, and results in social withdrawals, which further leads to psycho physiological stress. They also found that people at risk of schizophrenia have impairments in neuro cognition (attention problems, impaired working memory and executive functioning, all of which they refer to as "cognitive insufficiency"). This insufficiency can lead to poor performance, which leads to increased stress. They believe that greater stress contributes to delusions and hallucinations by increasing corticosteroid production (Beck and Rector 2005). They claim that a lack of integrative processes hinders other functions including self-reflection, self-monitoring and misunderstanding correction, leading to erroneous views. Insight and reality testing are both hampered.

Another study published in Cambridge University suggests that a cognitive–behavioural therapy intervention in the treatment of schizophrenia is effective

(Morrison 2009). A total of 422 patients with schizophrenia were recruited for comparison of treatment with CBT and standard treatment. CBT was given to 257 patients. The majority of patients were pleased with the program, with roughly 57% stating that it "has helped me more than anything else to comprehend my illness". One-third of the 132 patients who completed the survey received maximum points, resulting in a median total patient satisfaction score of 44 out of a possible 49. Over three-quarters of the 45 carers who completed the survey said they were satisfied with the program. The median total satisfaction score for caregivers was 47 out of 49. When the two groups were compared at the end of the intervention, there were no significant differences in symptoms of schizophrenia or the burden of care. Furthermore, there was no discernible difference between therapists, who provided an acceptable high-quality intervention. By the end of therapy analysis, there was a non-significant 3% improvement in the group of patients who had a carer involved compared to those who did not have a carer involved, showing no unique benefit (Turkington et al. 2006).

14.8 Methodology

The study was conducted to find out the improvement in cognitive and social functioning of patients of schizophrenia after psychosocial rehabilitation which includes cognitive training, social skill training and psychoeducation of family over a duration of 12 months. The study was conducted with two rehabilitation centres of Haryana compared with baseline score of the patient before intervention. A single case experimental design will be followed in the present study where age and gender are independent variables. Apart from this, the meta-analyses of more than 80 studies published on rehabilitation of schizophrenia were reviewed and the results were compiled.

14.9 Sample

The pilot study was conducted between January 2019 and January 2020 on 20 participants who were diagnosed with schizophrenia and are on medical rehabilitation from Haryana state. Four participants are students aged between 17 and 25 years, 16 participants are above 25 years of age, 12 participants are male, and eight are female belonging to sub-urban and urban locations. Out of 12 male patients, two male patients are uneducated; out of eight female patients, two female patients never attended any formal schooling; out of 12 male patients, six are working male and two male participants are in college; out of eight female patients, two are in college, six are homemaker, so all the eight are unemployed. Fourteen participants were married, and six were unmarried. Potential cases of substance abuse schizophrenia were omitted. All of the patients had a mix of good and negative symptoms. Seventeen

out of 20 show cognitive impairment. All the 20 participants show functional impairments.

14.10 Conduction

The persons with schizophrenia were assessed on structured interview with patient and family as per *DSM V* criteria with MMSE tool. The results of cognitive deficit and social deficit were recorded before starting the rehabilitation interventions and compared after 1 year of ongoing interventions. The gathered data was analysed for descriptive results on IBM SPSS, and the results were shared with the rehabilitation counsellors for the evaluation of practical interventions.

The participants when entered in study were having cognitive impairment and social impairment.

Fifteen out of 20 (75%) patients showed definite cognitive deficit (who score below 22), two out of 20 (10%) showed possible impairment (who score below 25), and three out of 20 showed no cognitive impairment. All the 20 participants were showed social impairment as these social issues persist after regular treatment and contribute to long-term functional impairment.

14.11 Interventions Given Over a Period of 12 Months

Social skill trainings and cognitive remediation were given to the participants according to their needs. CBT and psychoeducation are provided to the patients and their caregivers.

14.11.1 Social Skill Training

Social skill training by means of behaviour modification techniques were given to the participants to make them learn how to communicate their emotions, how to regulate emotions, how to participate in the community at the time of crisis. For this, the individual plan is prepared according to their immediate and long-term needs (Nakagami et al. 2008). During this process, the client and family were included for following procedures:

1. "Identification of the individual problem"—this process is done with the patients themselves if they are having insight about the barriers and their own obstacles in the current life, otherwise family is involved with problem identification.
2. "Goal setting"—This phase involves the setting of long-term goals for barrier removal, and its achievement can be time bound, and according to the amount of

difficulty, the patient is having the goal can be cut down into small task and short term goals.

3. "Behaviour techniques"—every individual undergoes behaviour rehearsal/role modelling approach in which patients exhibited verbal, nonverbal and paralinguistic skills necessary for effective societal interaction, and on completion of behaviour practice, the reinforcement was provided in the form of token (stars) as motivation reward.
4. "Group therapy"—this was introduced as a part of social rehab, in which the patients are allowed to interact with each other and allowed to express their feelings (which were learned in behaviour therapies) as a part of communication, in this they learn how to start conversation, how they can maintain, how to terminate it, and how they can work in the real world.
5. "IVAST"—in vivo amplified skill training is also introduced with family of the participants, in which therapist created few opportunities within the community setup for utilization of learned skills in the clinical setting, like for severe impaired patients. Family members were trained how to give the patient opportunities to improve his or her skills.

14.11.2 Psychoeducation

Psychoeducation is provided to the patients and their family members. Everything about the illness, its symptoms, causes of schizophrenia, truth and myths about schizophrenia, early warning signs of relapse, triggers of stress, role of family in therapeutic process, recovery process, prognosis and rehabilitation expectations were discussed with the family, and rehabilitation framework is made with the help of patient, family and therapist. The Problem Solving and support giving approaches were discussed with the family, relapse management and stress management strategies we told to the caregivers, with this burden of caregivers also discussed during the sessions and as it is observed, those people needs less hospitalization whose family participates in rehabilitation programmers (Kopelowicz et al. 2003). In this, patients learn about the symptoms and coping mechanisms, families understand the needs of the patients and learn the ways to help them in time of crisis. Family was educated with the help of electronic literatures and counselling methods. Relaxation techniques were shared with the caregiver, two sessions per month were given to the family, and continuous feedback was taken.

14.11.3 CBT

Cognitive behaviour therapy is a therapeutic strategy for mood and anxiety disorders that integrates cognitive and behavioural therapies and has high empirical evidence. CBT believes that while emotions are difficult to change directly, they can be

modified if we try to change the thought that causes the distressing emotions. CBT develops a set of skills that allow a person to be aware of their thoughts and emotions, identify how situations, thoughts and behaviours influence emotions, and improve feelings by changing dysfunctional thoughts and behaviours (Tarrier and Haddock 2004). It has been observed that negative symptoms are the primary cause of functional impairment in schizophrenia; to address this, CBT therapies for schizophrenia have been proposed. CBT skill acquisition is a collaborative process. CBT differs from "talk therapy" in that it emphasises skill acquisition and homework assignments. Initialy Insight oriented questions were asked and it should be find out how much problem contribution is there due schizophrenia for that particular participant in his personal and professional life after that the therapy is planned, the person who is having insight about his sues can benefit more with CBT otherwise CBT is not proved to be very effective for reducing positive symptoms but it shows reduction in negative symptoms and relapse in the current study 20 participants with schizophrenia were enrolled for 4 session per month, after 12 months 45% participants (9 patients) were satisfied and leant about their emotions and feelings and shows visible less negative symptoms.

These sessions were planned according to individual need and according to the education and cognitive levels of the participants. For the reduction of positive symptoms, "peripheral questioning" is used. It is a procedure in which the person is questioned about the details of his or her delusional ideas in order to comprehend how he or she came to this conclusion. Skills are taught during sessions, and homework assignments are assigned, such as:

1. List down the questions you have for therapeutic process and bring in the next session.
2. Use the given CBT model to describe your situation.
3. Write down the things you like about previous session, and what you wish to change about previous session.

Three-column thought form was given, which they can fill it after their positive symptoms. This homework is optional for the patients, otherwise it will be filled by the carers. These are few examples from CBT modules used in schizophrenia.

14.11.4 Cognitive Remediation

As we know the cognitive impairment plays a major role in functional disability. According to this study, out of 20 patients with schizophrenia, 75% (15) have cognitive impairment and require cognitive remediation. Cognitive remediation is a behavioural therapy that improves cognitive processes with the goal of durability and generalization. Different interventions based on these concepts have been created and used since its inception, with significant differences in structure, setting and scheduling. It aids in strengthening thinking skills such as attention, working memory, planning and executive function. Cognitive remediation is used for the restoration of

declining cognition as well as enhancement of cognitive process in people with schizophrenia (Wykes 2004). It helps in increasing attention and concentration. It works on memory and distorted thinking process too (Wykes et al. 2011). The sessions are planned as 12 sessions per month. The methods for improving cognitive function by repeating cognitive activities and/or learning new strategies started with sorting, coin sequencing, matching flash cards to provide more structured computerized training over a period of time. Apart from this, focus switching attention, attention narrowing, increased activity levels, social engagement, self-statement alteration and internal conversation were also introduced using specific cognitive and behavioural strategies. The instruction was provided by a cognitive therapist for a period of 12 months, and the subjects were examined using the MMSE.

14.11.5 Meta-Analyses of Published Data

The meta-analyses of previously published studies are also compiled which will support the results of the above study for which electronic database was searched for studies on individual cognitive and social rehabilitation and integrated rehabilitation methods used for the treatment of people with schizophrenia. The results are compiled in Table 14.1.

These studies were conducted between 2011 and 2018. The studies included the results of individual rehabilitation approach on the people with schizophrenia and

Table 14.1 Results of study conducted on 20 people with schizophrenia over a period of 12 months

Therapy name	No. of patients enrolled	No. of patients attended	Sessions/ month	Results	Satisfaction	No. of patients satisfied
Social skill training	20	20	12	Improvement in activities of daily living, self-help, self-medication	60%	12
CBT	20	20	4	Less negative symptoms observed	45%	9
Psychoeducation	20	20	2	Reduction in hospitalization and relapse rate Increase in treatment compliance	50%	10
Cognitive remediation	20	20	12	Improvement of cognitive functioning	35%	7

the effect of combination of two or more approaches. All the studies support the integration of medical interventions with psychosocial interventions. No study claims to achieve significant elimination of positive or negative symptoms, but studies shows that community-based rehabilitation along with medications are able to manage the symptoms well and significantly improved the quality of life and functional capacity of people with schizophrenia (Harvey and Strassnig 2012).

14.12 Results and Discussion

14.12.1 Social Skill Training

In the current study, 20 participants attended the social skill training through behaviour modification techniques. Twelve sessions per month were planned for each individual. Initially, the individual sessions were given after few weeks of group sessions. Out of 20, 60% (12) of participants show improvement in functional capacity. Improvement in independent travelling to the market, making decisions for themselves, improvement in self-help and self-medication, which further improved treatment compliance. Coming to therapist without any caregiver's support is another achievement shown by few individuals; purchasing groceries from the market and increased contribution in the work front are also noticed.

14.12.2 Psychoeducation

In the current study, 20 caregivers/participants enrolled for psychoeducation for two sessions in a month for 12 months, and 50% of participants show improvement in the knowledge about the schizophrenia and are able to handle the stress related to schizophrenia effectively at home. Less relapse rates and more treatment compliance are observed. The results are more qualitative and are based on the reviews during psychoeducation and caregiver counselling sessions.

14.12.3 CBT

In the current study, 20 participants with schizophrenia were enrolled for four session per month. After 12 months, 45% of participants (9 patients) were satisfied and leant about their emotions and feelings and show visible less negative symptoms improvement in social skills, and functional capacity increases with increase in more participation in the family, less co-morbid depression, and somewhat less episodes of positive symptoms.

14.12.4 Cognitive Remediation

The results were analysed on Anova and show improvement in the cognition with effective size ($d = 0.43$). Now only 50% of participants show the score below 22, indicative of cognitive deficit on MMSE out of 20. Twelve participants are able to enhance the cognition while eight participants were on their initial score only and seven participants improve to no cognitive deficit range.

No. of participants	Cognitive impairment	Possible impairment	No impairment
20	15	2	3

Result after 12 months of cognitive remediation along with social skill training and other psychotherapies

No. of participants	Cognitive impairment	Possible impairment	No impairment
20	10	3	7

14.13 Meta-Analyses of Previously Published Studies on Rehabilitation of Schizophrenia (Table 14.2)

The results of 30 research studies on the effect of cognitive behaviour therapy on schizophrenia included the results of interpersonal therapy too conducted on more than 1500 patients for the duration of 12 months, generally 2–4 sessions in a month It shows significant improvement in social functioning, reduction in positive and negative symptoms, increase in insight, decrease in depression associated with schizophrenia, with overall increase in neurocognitive functioning and decrease in psychosocial stress levels, with reduction in suicidal rates and reduction in hospitalization rates with effective size ($d = 0.51$).

Similarly when we analyse the efficacy of social skill training on schizophrenia, and behaviour therapy for schizophrenia, 20 similar studies with more than 700 participants were analysed with moderate to large effective size ($d = 0.76$) which shows more positive results of social skill training on the improvement of quality of life of people with schizophrenia; the participants who enrolled for social rehabilitation showed improvement in psychosocial functioning, independent functioning, less care required from caregivers, and also showed reduction in relapse and better treatment compliance. Similarly it has been observed from 20 similar studies on effect of psychoeducation on the people with schizophrenia and their caregivers that 20% improvement in the relapse rates, measured on the bases of less hospitalization requirements, with more support from the family, and better understanding of the symptoms results in less panic situation at home, more treatment compliance, less treatment withdrawn were observed, few caregivers are reported to be trained to provide psychological first aid to their patients in adverse situations and better

Table 14.2 Five meta-analyses of previously published studies on rehabilitation of schizophrenia

Name of CBR	No. of studies/no. of participants	Duration of study	Effectiveness	Results
Cognitive behaviour therapy	30/1504	9–12 months	Reduction in symptoms, improvement in social functioning	Moderate ES ($d = 0.51$)
Social skills/ behaviour therapy	20/702	9–12 months	Improvement in social cognition and improvement in psychosocial functioning	Moderate to large ES ($d = 0.76$)
Cognitive remediation	10/160	12–24 months	improvement in neurocognitive functioning attention/memory	Large mean ES ($d = 0.53$)
Psychoeducation to family	20/406	6 month	reduction in hospitalization, improved compliance	20% reduction in relapse

management of stress, and with the help of relaxing techniques, the overall quality of family life is also improved after psychoeducation programs.

With analyses of 10 studies with keyword cognitive remediation of schizophrenia, which were conducted on more than 160 patients of schizophrenia with cognitive impairment, cognitive interventions were provided for 12–24 months with 3–5 sessions in a week, with effective size of $d = 0.53$, which showed improvement in neurocognitive functioning, increase in attention and concentration span, improvement in memory, registration and orientation. Few develop self-analyses, and few reported about the improvement in judgement and insight levels.

14.14 Conclusion

Schizophrenia is defined by substantial deficits in reality perception and behavioural alterations associated with persistent delusions, persistent hallucinations, disordered thinking, and disorganized thinking. When combined with medical therapies, people with schizophrenia frequently have chronic challenges with their cognitive and social abilities, resulting in functional disability. The rehabilitation process has been shown to improve the symptoms of schizophrenia. The subjective model of recovery and rehabilitation methods have similar values. Rehabilitation therapies have been established to improve functional outcomes and encourage recovery. They promote active engagement in the fight against the condition with self-determination and empowerment. More research is needed to pinpoint the effects of cognitive remediation. Factors such as motivation and social cognition may play an active role in interventions.

Psychoeducation for patients and their family has been shown to be useful in avoiding relapses, readmissions, and boosting drug compliance. Social skill training

has been shown to be highly effective when combined with cognitive remediation and behaviour modification, which is why the three rehabilitation interventions are frequently combined. In addition to allowing patients to practice newly acquired skills in everyday situations, it also provides appropriate feedback and social reinforcement.

The literature evidence on CR is rather consistent, indicating that CR in combination with CBT is effective in lowering positive symptoms. As a result, integration of medical rehabilitation and community-based rehabilitation tailored to the individual needs of the patient and family has proven to be more effective than medical or psychosocial rehabilitation alone in terms of effective and long-term management of schizophrenia. It should also be noted that all of these interventions are always delivered within the context of rehabilitation and are not intended to be stand-alone therapy. Several program combining therapies, such as CBT and skill trainings, CR and social skill training, or cognitive training and CBT and skills training, as well as psychoeducation of family members, have proven to be effective in increasing treatment adherence.

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Chapter 15
Consumption of Cannabis: A Risk Factor or a Therapeutic Agent for Patients with Schizophrenia

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15.1 Schizophrenia

15.1.1 Introduction

Schizophrenia is a chronic and severe condition that affects about 1% of the population and is thought to also have a neurodevelopmental basis. The ailment sets its course in the adolescent years, and many people suffer from it for the rest of their lives. As a diverse condition, everyone's symptom expression is generally distinct; however, symptoms are typically grouped into three classifications:

- Positive symptoms (hallucinations that are auditory and visual in nature (Chatterjee et al. 2019), misapprehension, and disorganized thinking),
- Negative symptoms (detachment, lack of interest, depression, and social withdrawal) and
- Impairments in cognition (dysfunctional execution, processing and communication in brain region, diminished working) (Dunn et al. 2020).

15.1.2 Course of the Disease

The course of schizophrenia can be divided into four stages:

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First stage manifests characteristics of genetic vulnerability and environmental risks, which can be determined with family history.
Second stage includes behavior of seeking help, which can be detected by a psychiatric examination.
Third stage is behavioral repetition, which can be detected by clinical discussion.
Fourth stage is demonstrated by loss of functions of the individual which can also be diagnosed by clinical interviews (Bansal and Chatterjee 2021).

15.2 Epidemiology of Schizophrenia

Schizophrenia usually develops before the age of 19 in around 39% of male and 23% of female patients. The peak incidence age is approximately 14 years and it falls between the ages of 15–25. The subthreshold of occurrence is greater in late childhood and adolescence as compared with adulthood. Hence, adolescence is the most crucial age group for the incidence of psychosis (Patel et al. 2021).

15.3 Cannabis

15.3.1 Introduction

Most well-known species of a flowering plant; cannabis known as *Sativa*, *Indica*, and *ruderalis*. In its dried plant bud appearance, it is called "Marijuana." In its block form, plant resin is called "Hashish." Some of the biologically active molecules that also define different qualities of this cannabis strain are flavonoids, cannabinol, terpenoids, and cannabinoids. There are different 100 forms of cannabinoids, the two familiar and medically appropriate are delta-9-tetrahydrocannabinol (THC), the essential psychotropic agent of cannabis, and cannabidiol (CBD) which has anti-inflammatory characteristics. THC partially activates the cannabinoid receptor, while the CB1 receptor negative allosteric modulator is CBD (Urits et al. 2020).

15.3.2 Risks of Smoking Cannabis

Marijuana is the most used illegal drug on the planet. After alcohol and cigarettes, it is the most widely used substance on the planet. In 2015, more than 11 million individuals in the age group of 18–25 consumed cannabis making it the most extensively consumed illegal drug in the United States of America (NIDA 2016). As with any drug, there are hazards connected with its usage; some of these concerns are related to the substance itself, while others are dependent on the medication's regulatory status in the individual's local jurisdiction. The most well-known risk

related to the consumption of cannabis is the chance of developing psychosis. Cannabis consumption is linked to psychotic-like symptoms, which have been well documented in the literature such as delusions and hallucinations (Hamilton and Monaghan 2019; Ortiz-Medina et al. 2018).

15.4 Association of Cannabis with Schizophrenia

15.4.1 Background of Cannabis-Associated Psychosis

The Swedish Conscript Study, conducted in 1969–70 lasting more than 10 years, focused on larger than 45,000 fresh entrants in the military who were followed up immediately, providing the first documented evidence linking cannabis consumption to schizophrenia. According to the findings, people who consumed cannabis before the age of 18 had 2.4 times more chance of getting infected with schizophrenia than those that have never consumed it. The likelihood of acquiring schizophrenia was linked to the frequency with which it was used (consumption on more than 50 occasions) (Andréasson et al. 1987).

15.4.2 Use of Cannabis and Psychosis

In a study with 247 patients hospitalized for the first phase of psychosis, 194 patients responded with a "yes" to marijuana consumption and revealed smoking more than 5 joints in their life span (Birnbaum et al. 2019).

Cannabis consumption on a regular basis raises the chance of psychotic consequences; however, there is a drug concentration relationship between consumption and psychosis risk. As a result, part of the relationship among cannabis consumed psychosis may reflect the fact that people who smoke cannabis have a higher chance of onset of psychosis, and there may not always be a causal connection underlying cannabis consumption and the pathophysiology of psychotic events in these individuals (Alderson et al. 2017).

A meta-analysis of various studies with 4036 total participants reveals an association between smoking marijuana with the incidence of psychosis (Marconi et al. 2016).

A meta-analysis of 41 papers comprising 98 organizations indicates a link with consuming cannabis and a higher chance of developing schizophrenia spectrum disorder without evidence of bias (Belbasis et al. 2018). In the Western world, 10–20% of the population consumes marijuana whereas 30–50% of people with schizophrenia consume marijuana (Barnett et al. 2007; Fowler et al. 1998).

The use of the emergency department (ED) for mental health problems following the legalization of cannabis in Canada has not been fully investigated but literature is available that studied the issue is beginning to appear in this area. On October

17, 2018, recreational cannabis was officially approved for consumption after regulating the use of marijuana for medical purposes since 2001. Negative estimates of the risk of disease in Canada reveal a few marijuana-related cases that makes an average of 106–186 schizophrenia cases caused by marijuana in Canada annually (Fischer et al. 2016).

The purpose of this chapter is to investigate the link between cannabis consumption and the development of schizophrenia disease.

15.5 Mechanism of Action of Cannabis

Cannabinoid receptors (i.e., CB1R) have G-protein-coupled sensors (GPCRs) that show the impact of tetrahydrocannabinol (THC; the main psychoactive component of cannabis) and endocannabinoids on central nervous system function. The modes of action are still being unraveled. The endocannabinoid network is indeed a ligand that communicates retrogradely and includes cannabinoid receptors (CB1r/CB2r), found naturally indigenous ligands including 2-arachidonoylglycerol anandamide, and enzymes that synthesize and degrade these ligands. This system has an impact on neurodevelopment, appetite, mood, and memory, among other things (Perez et al. 2019).

15.6 Cannabinoids and Nervous System Tissues

15.6.1 Receptors on Central and Peripheral Tissues

Cannabis (Cannabis sativa) consists of various cannabinoids that operate on central and peripheral tissues via the endocannabinoid system. The psychotropic activities of these cannabinoids are frequently described in terms of whether they modify an individual's mood, consciousness, and/or perception. Endocannabinoids, which limit propagation from both glutamatergic and GABAergic terminals retroactively, activate most of the cannabinoid receptors, which are found in the presynaptic terminals (Dunn et al. 2020).

15.6.2 Oxidative Stress and Advanced Glycation (AGEs) Levels

Excessive oxidative stress is linked to schizophrenia. Oxidative stress is connected to the development of advanced glycation (AGEs) in the skin. Increased skin AGE levels have been found to introduce psychosis and persistent schizophrenia.

Cannabis usage is linked to AGE accumulation, which results in higher amounts of pro-inflammatory cytokines that are harmful to mitochondria, as well as increased oxidative stress caused by tetrahydrocannabinol (Hagen et al. 2020).

15.7 Theories Related to the Link Between Schizophrenia and Cannabis Use

In recent literature, four ideas have been presented to account for the possible connection between the use of cannabis with schizophrenia:

1. While acute and temporary psychosis can occur after cannabis consumption, altogether, most of the cannabis smokers do not suffer a psychiatric disease. According to the interaction theory, Individuals who have a genetic or environmental predisposition to schizophrenia, on the other hand, are extremely vulnerable to the drug's side effects, which can lead to the development of a psychotic condition.
2. The other drugs or "gateway drug" hypothesis proposes that consumption of cannabis is frequently linked with the consumption of other substances such as alcohol and tobacco, also psychotomimetic drugs like phencyclidine or amphetamine (Fergusson et al. 2006), and thus, the higher chance of onset of schizophrenia may be due to such substances instead of cannabis (Fergusson et al. 2006). While other drug usage is taken into account, cannabis still increases the risk of schizophrenia.
3. The causal link theory argues that cannabis consumption raises the likelihood of getting psychosis. According to current studies, the quantity and time of the very first period of use impact the severity of this effect (Di Forti et al. 2014). Frequent cannabis consumption and initiation of usage too early are interlinked with a higher chance of psychosis conversion; however, lifelong consumption is not.
4. The surprising hypothesis posits that single or even more common pathways determine how likely a person is to take cannabis and acquire schizophrenia, for both having common basic genetic bases and resulting in separate phenotypes. The link between schizophrenia and cannabis usage has been discovered thanks to overlapping genetic variations, according to genome-wide association studies (GWAS).

   The impact of consumption of cannabis and the emergence of psychotic manifestations has indeed been researched in a variety of studies, with the reliability of data demonstrating that cannabis use causes psychotic symptoms and is a causal component in the growth of schizophrenia (Wilkinson et al. 2014). Increasing amounts of evidence show a link between the history of use of cannabis and incidence of mental illness later on, but not otherwise (van Os et al. 2021).

15.8 Factors Affecting the Association of Cannabis and Schizophrenia

Certain factors are thought to influence the chance of developing schizophrenia as a result of cannabis usage, including:

15.8.1 Dose

Taking cannabis on a regular basis may raise the risk of psychosis. Therefore, the existence of cannabis dependence would be linked to the number of intakes. Whenever the amount of consumer lifetimes exceeds 50, the risk elevates (Evins et al. 2012).

15.8.2 Age of Onset

Another key consideration is the age at which consumption began. Early intake, even before age of 15, is linked to a higher likelihood of experiencing psychosis and is hence more hazardous. Furthermore, the younger the age at which cannabis dependence develops, the greater the chance of acquiring psychotic manifestations (Evins et al. 2012).

15.8.3 Sex (Gender)

Consumption of cannabis and the formation of psychotic manifestations or psychosis are interlinked and gender has no bearing. The bulk of research, however, contains a higher number of male patients. This appears to have hampered our knowledge of the relationship involving cannabis and schizophrenia in women (Evins et al. 2012).

15.8.4 Genetic Predisposition

There are different genes that are responsible for the onset of schizophrenia. Scientific research recognizes 108 genes in total that carry the risk of incidence of schizophrenia. Receptors of dopamine, immunity network, synaptic plasticity, and glutamate transmission are some of the recognized genes (Chatterjee and Mittal 2019).

Cannabis consumption multiplies the risk of incidence of psychosis, and there is a multifactorial gene-environment interplay that would amplify this link in sensitive individuals. Most people who consume cannabis will not acquire a psychotic disease at all, and it is thought that the connection between cannabis consumption and psychosis onset involves a genetic vulnerability linkage.

Frequent cannabis consumption previously to the development of illness could be made in an effort to treat premorbid manifestations, culminating into a vicious loop that contributes toward raising pathology in people at risk biologically. CNRIP1 expression changes may be responsible for the pathophysiology underlying schizophrenia. Indeed, alterations in CNRIP1 activity may raise a person's risk of developing schizophrenia (Evins et al. 2012).

In a study including first-episode psychosis (FEP), patients and population control were recruited to investigate gene-environment interactions (EU-GEI). Only a small percentage of cannabis consumers emerge with a full-blown mental illness, and the results reveal that the consumption of marijuana influences the SZ genetic link in shaping psychopathology in the onset of psychosis (Quattrone et al. 2021).

15.8.5 Environmental Risk

The incidence varies from region to region (e.g., higher in certain urban versus remote regions) and social circle (e.g., higher sometimes in minority ethnic groups), but there is latest significant evidence indicating a few environmental risk factors, including childhood trauma and cannabis use, in relation to well-established hereditary and neurobehavioral risk factors (Evins et al. 2012).

Lifestyle has a prominent role in the incidence of schizophrenia. The occurrence of schizophrenia has also been associated with a deficiency of some vitamins. A study has indicated lower levels of vitamin C and vitamin E in individuals that smoke cannabis as compared with non-smokers. Vitamin E causes the release of serotonin and vitamin C is vital to the functional immune system. Therefore, the deficit in vitamin C, vitamin E and serotonin levels may lead to the occurrence of various neurodegenerative diseases, i.e., schizophrenia (Bleich et al. 1988; Ogbodo et al. 2019; Bansal and Chatterjee 2022).

15.8.6 Comorbid Substance Use

Cannabis is commonly consumed with tobacco; researchers have focused on their synergistic effects on psychosis. Tobacco seems to be a potent risk factor for psychosis on its own. Cigarette smoking rates among people with psychosis are higher than in the general population, reducing cigarette usage in this group would have apparent overall health advantages (Evins et al. 2012) (Fig. 15.1).

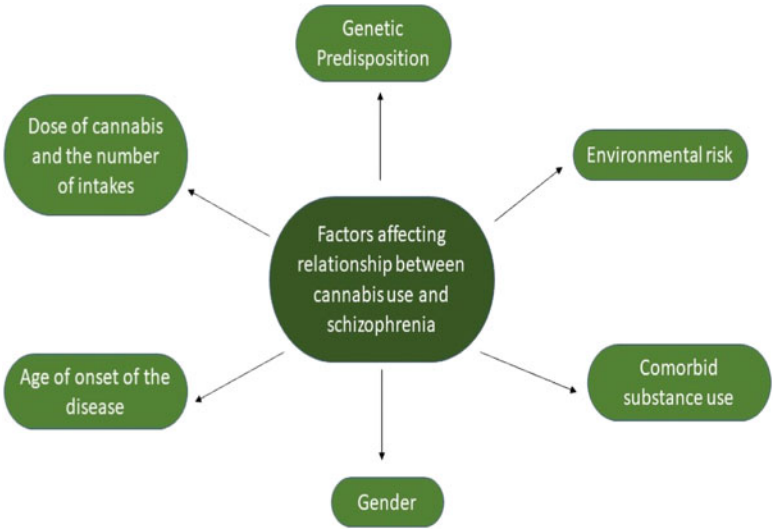

Fig. 15.1 Factors affecting the association between cannabis consumption and onset of schizophrenia

15.9 Cannabis-Induced Psychosis and Schizophrenia

15.9.1 Substance-Induced Psychotic Disorder

According to recent research, some patients with SIPD (substance-induced psychotic disorder) experience symptoms at a higher incidence than would be expected. There is substantial evidence that frequent consumption of psychoactive drugs is connected to the evolution of schizophrenia in vulnerable individuals, particularly cannabis usage showing the strongest link. Cannabis-induced PD (psychotic disorder) has one of the lowest onset ages and the greatest rate of conversion to schizophrenia.

Cannabis-associated SIPD had the earliest age of onset, the largest likelihood of conversion to schizophrenia, and the highest first rank symptoms when compared to the other subtypes. Schizophrenia risk was the same in converted cannabis SIPD cases as in conventional schizophrenia cases (Zhornitsky et al. 2015).

15.9.2 Conversion of Cannabis-Induced Psychosis to Schizophrenia

A study found that schizophrenia disease may be prevented in about 8–13% of the patients if cannabis intake was avoided (Kendler et al. 2019).

Another study showed that 23% of patients with drug-induced psychosis were diagnosed with schizophrenia within 3 years of follow-up (Chen et al. 2015).

A study reports that approximately 50% of cannabis consumers that present in ED that have been hospitalized for marijuana-induced psychosis will continue to develop schizophrenia (Niemi-Pynttäri et al. 2013).

Psychosis caused by marijuana appears to translate into schizophrenia in up to 50% of cases. One study showed that patients with drug-induced psychosis often had a family history of substance abuse and were found to be diagnosed at an older age than patients with primary psychosis (Caton et al. 2005).

There is also a study that revealed that 47.4% of the patients that suffer from psychosis induced by cannabis were converted into schizophrenia and had an almost double the chance of mutation as compared to other psychiatric disorders caused by cannabis. The hypothesis that there is a direct link between cannabis and schizophrenia is also based on the evident dose-response relationship found between marijuana consumption and the occurrence of schizophrenia. This means that a small number of patients who have had drug-induced mental psychosis are at greater risk of experiencing schizophrenia. Self-harm capability was also seen in these patients (Starzer et al. 2018).

Drug use disorders, especially marijuana, amphetamines, and opioids, may be related to the conversion of schizotypal disorders to schizophrenia. However, conversion rates are high even for those who do not have substance abuse disorders (Hjorthøj et al. 2018).

15.9.3 Cannabis-Induced Psychosis and Genetics

Research may allow for genetic testing, for example, whether endocannabinoid genes affect the psychosis caused by cannabis, or whether genes that influence the striatal dopamine response cause some people to be more prone to childhood adverse reactions to psychosis. Early risk factors such as ethnicity, adversity, and marijuana consumption are also partly responsible for determining the outcome. On the contrary, if the etiological element is not removed, e.g., by ceasing the consumption of high potency cannabis, the effect can be much better (Murray et al. 2020).

15.10 Effects of Cannabis on Brain Function

15.10.1 Endocannabinoid System

Endocannabinoid (eCB) networks are engaged throughout neuronal development, modulating a variety of neurodevelopmental processes such as adult neurogenesis, axonal guidance, cortical interneuron placement, neurite outgrowth, and morphogenesis (Song et al. 2021). Grey matter loss, myelination, rewire, reduction in synapses and dendrites, and changes in neurotransmitter ratio are all key brain maturation processes that occur during adolescence. These alterations in the eCB

system within the period of adolescence suggest that the system is implicated in central nervous system development and also that engagement by external THC (an active ingredient in cannabis) may impair this development, which can be explicitly or implicitly, either way, decrease CB1R signaling via indirect regulation mechanisms.

15.10.2 CB1 Receptor in the Brain

The cannabinoid receptor named CB1 is the primary receptor found in the brain, and studies suggest that disruption in the regulation of the CB1 receptor in various brain areas, is involved in the onset of schizophrenia by undermining complex networks that indirectly connect cognition and memory (Seillier 2021). The receptor named CB1 is found in both central and peripheral tissues and is encoded by the CNR1 gene. CNR1 genetic variations have been linked to altered clinical manifestations of schizophrenia in cannabis-exposed individuals. Heavy cannabis consumption in conjunction with prominent CNR1 genotypes may lead to deficits in the size of white matter and cognitive dysfunction in patients with schizophrenia (Ho et al. 2011). In a recent study, CB1 receptor availability was found to be lower in male patients that experienced the first event of psychosis, and lower levels of CB1 receptor were linked to impaired cognition and severity of symptoms (Borgan et al. 2019).

15.10.3 Chronic Cannabis Use and Brain Changes

Research conducted with brain imaging has demonstrated that persistent consumption of cannabis leads to changes in the brain. The regular cannabis consumers indicate the consistently diminished size of grey matter, specifically brain areas that have increased CB1R levels, such as the cerebellum, amygdala, prefrontal cortex, and hippocampus. Mature cannabis consumers had higher stimulation in brain areas, i.e., both superior and posterior transverse temporal region and inferior frontal gyri and diminished stimulation in the striate region, insula, and middle temporal gyrus as compared with young healthy individuals, on the other hand, young cannabis consumers had higher stimulation in brain regions like putamen and subordinate parietal gyrus (Krebs et al. 2019).

Strong evidence suggests that hippocampal/parahippocampus atrophy in patients with chronic psychotic disorder, first-episode patients had a higher chance of experiencing psychosis. Similarly, investigators reported a correlation between prolonged marijuana consumption and cortical degeneration. The uncus, a region below the hippocampus/parahippocampus, is responsible to cause both positive (hallucination) and negative (social withdrawal) psychological symptoms and may be involved in cannabis-related psychotic-related experiences. A small increase in

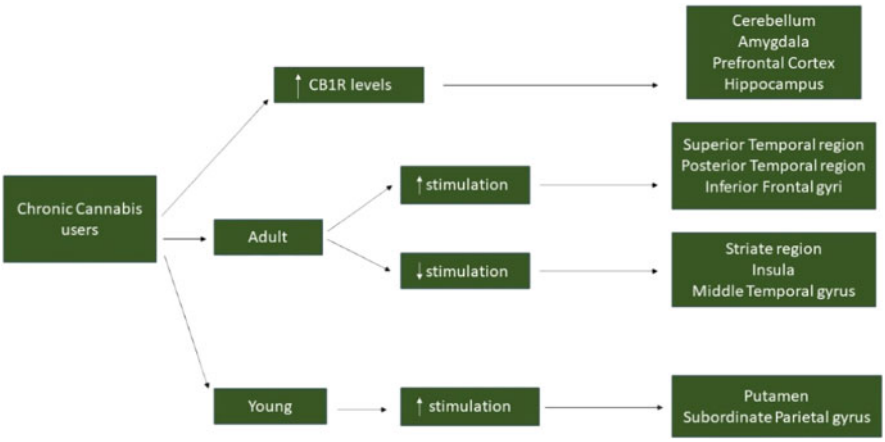

Fig. 15.2 Brain changes in chronic cannabis users

uncus volume was observed and it can be inferred that it may be one of the pathophysiological mediating links between cannabis consumption and psychological effects. This view is supported by strong evidences: first, CB1 is mainly expressed in the olfactory lobe region, hippocampus, parahippocampus, and amygdala, second, reduced congestion and increased glial cell regeneration, and third that functional study with the cross-sectional neuroimaging structure reports the interaction of hippocampal atrophy that uses marijuana for a long time (Quattrone et al. 2021) (Fig.15.2).

15.10.4 Acute Cannabis Consumption and Brain Changes

Acute cannabis consumption is related to a modest improvement in the release of dopamine from the corpus striatum, while prolonged cannabis consumption results in reduced release of dopamine and also reduced CB1 receptors, according to neurochemical imaging studies (Krebs et al. 2019).

15.10.5 Genetic Risk in Adolescence

Adolescence marijuana consumption carries an increased risk of incidence of schizophrenia as well as psychosis (Arseneault et al. 2004; Bechtold et al. 2015). Adolescent marijuana exposure contributes to the etiology of schizophrenia only in people who have a genetic susceptibility (Henquet et al. 2005; French et al. 2015). The hypothesis is justified by a longitudinal study that revealed that patients who

have prominent catechol-methyl-transferase polymorphisms carry a higher risk of the onset of schizophrenia in teenagers who smoke cannabis (Caspi et al. 2005).

15.10.6 THC Delta-9-Tetrahydrocannabinol

There have been reports on the connection between the intake of an active component of cannabis, THC, and increased release of dopamine. Ironically, however, prolonged cannabis consumption and premature births are linked to the diminished release of dopamine from the striatum. There is a possibility that a dopamine receptor stimulation or dysfunction due to trauma may be one way in which different exposure is combined with genetic risk to provide a higher risk of schizophrenia (Stilo and Murray 2019).

15.10.7 Changes in Corpus Callosum

Cannabis is partially responsible for inducing psychosis in individuals who suffer from neurodevelopmental disturbances. On the contrary, this is not observed in general cases of psychosis in normal patients. The possible explanation for this finding can be that consumption of high potency cannabis can damage the microstructural arrangement of the corpus callosum (Rigucci et al. 2016).

15.10.8 Electroencephalography (EEG) Studies

It is interesting to note that electroencephalography (EEG) studies have shown that long-term cannabis consumption impairs the brain's potential to give rise to brain waves (beta and gamma-band activity). (Hajós et al. 2008; Kucewicz et al. 2011; Skosnik et al. 2012). Brain waves are essentially responsible for regulating activity between brain regions and disturbance of contemporized neuronal capability can have an impact on a broad range of nervous functions. Long-term cannabis consumption causes the same disruptions in neuronal coordination which are observed in schizophrenia disease (Skosnik et al. 2016). Thus, it is indicated that the effect of cannabis on neuronal oscillations is responsible for the onset of schizophrenia (Uhlhaas and Singer 2010).

15.11 Cannabis Comparison with Other Drugs

15.11.1 Cannabis and Alcohol

Retrospective observational research was conducted on 124 hospitalized patients suffering from the schizophrenia spectrum. Lifelong violent behavior was analyzed using a History of Aggressive Behavior Form as well as the Positive and Negative Syndrome Scale. Drug abuse disorders were identified in accordance with the Diagnostic and Statistical Manual of Mental Disorders. Violent and non-violent psychiatric patients have shown similar increase in disorders induced by cannabis. Problems with alcohol and cocaine consumption were commonly found in mentally ill patients. Marijuana disorder was not linked to any addiction, and alcohol abuse was positively linked to uncontrolled physical activity as well as cocaine use and the tendency to become addicted. These findings suggest that marijuana and alcohol abuse are severely debilitated in mentally ill patients who have a tendency toward aggression, but at most alcohol is related to uncontrolled aggressive conduct (Comai et al. 2021).

15.11.2 Cannabis and Tobacco

Tobacco usage is closely connected with cannabis consumption in both observational and genetic research, and it has been hypothesized that tobacco acts synergistically with cannabis to induce addiction (Rabin and George 2015). Furthermore, cigarette usage has been demonstrated to alter the link between cannabis and psychotic symptoms, implying that controlling tobacco consumption lowers the cannabis–schizophrenia relationship (Gage et al. 2014).

15.12 Cannabis Consumption, Adolescence, and Schizophrenia

Marijuana consumption is very common among adolescents and teenagers which is also an important period for brain development. Cannabinoid receptors are located in glial cells and are believed to be responsible integrity of white matter functionality, commination, and interconnectivity. With the help of diffuse tensor imaging (DTI), numerous studies investigating neuronal strips have found a decrease in white matter stability across all temporal and anterior lobes in young marijuana consumers. Marijuana consumption on long-term basis causes impaired cerebrovascular function, which is linked to an increasingly higher chance of thromboembolic events (Suryadevara et al. 2017).

Marijuana consumption is linked to motivation and mental retardation and there is evidence to show the most significant effects when cannabis consumption begins in adolescence. Such factors may therefore influence the part played by cannabis consumption as a contributory factor for psychosis in all studies (Belbasis et al. 2018).

The age at which cannabis consumption appears to connect age with the onset of psychosis, whereas continued cannabis consumption after the first event of psychosis is linked to poor prognosis along with increased recurrent cases, positive symptoms, and extended hospital stays (Stilo and Murray 2019).

Collected data from 162 hospital records over a span of 2 years showed that drug use often complicates diagnostic clarity and the use of other substances such as cannabis and methamphetamine may present the same clinical picture as schizophrenia, especially in adolescents (Taukoor et al. 2017).

A study in KwaZulu-Natal found that schizophrenia was the most common disorder among psychotic adolescents on substance abuse (Paruk et al. 2009).

15.13 Outcome in Patients with SZ Smoking Cannabis

15.13.1 Prognosis

The consumption of cannabis is linked to more acute psychosis, more hospitalization, and a bad prognosis. Schizophrenia patients who consume cannabis continue to have a greater risk of recurrence, prolonged hospital stays, and much more extreme positive symptoms than previous consumers who stopped using cannabis or never consumed cannabis.

15.13.2 Adverse Effects and Cognitive Performance

Furthermore, patients with first-episode psychosis are more sensitive to both the good and adverse effects of marijuana than healthy controls, bolstering the case for a relationship between psychosis and marijuana. However, several studies have found that marijuana users suffering from schizophrenia had better cognitive performance than nonusers (Krebs et al. 2019).

15.14 Cannabis as Therapeutic Agent

15.14.1 Cannabidiol for SZ Patients

Some research shows that cannabis, in little dosages, can help with the manifestations of schizophrenia. Cannabis work by activating cannabinoid receptors, i.e., their types CB1 and CB2. CB1 receptors are found everywhere in the central nervous system and numerous peripheral tissues and organs. The location of CB receptors may explain how cannabis affects cognitive functions (Freund et al. 2003). Cannabis consumption on a regular basis was linked to improved cognitive function in people with schizophrenia. On tests of global cognition, visual memory, processing speed, working memory, planning, and reasoning, cannabis users fared somewhat better than nonusers. While superior cognitive performance in cannabis users compared to nonusers was only noticed in individuals who began using cannabis at a young age (Yücel et al. 2012). Cannabis produces key chemicals, for example, delta-9-tetrahydrocannabinol (THC) which is a psychotic substance and cannabidiol (CBD), which has partial antagonism characteristics (Atakan 2012; Mechoulam and Hanuš 2000; Pertwee 2008). CBD produces minor subjective effects and there are no euphorigenic features related to it, and it also affects the efficacy of THC; thus, there is a lot of research going on right now. These CBD characteristics may be effective in the treatment of psychosis and schizophrenia in people who also consume cannabis. It could potentially lessen cannabis consumption by reducing THC's psychotomimetic impact (Hahn 2018).

A study found that taking 1500 mg of CBD every day for 26 days can help those with treatment-resistant schizophrenia (Sarris et al. 2020). In another study, patients with stable schizophrenia spectrum diagnoses who took 1000 mg dose of CBD within 6 weeks in addition to antipsychotic drugs observed a drop in positive symptoms (Hoch et al. 2019).

A research project showed that giving schizophrenia patients 600–800 mg dose of CBD within 4 weeks reduced psychotic symptoms in the same way as Amisulpride (an antipsychotic medication) did, but with fewer adverse effects (Rohleder et al. 2016). Despite CBD's therapeutic potential, the low efficacy and safety of cannabis-based medicines necessitate further research.

15.14.2 Reduction in Symptoms of SZ

Most people with schizophrenia smoke marijuana in order to reduce their symptoms. It is noteworthy that while the consumption of marijuana for a brief period of time may reduce a few manifestations of this disorder, long-term marijuana consumption can have extended side effects. A number of studies prove that long-term cannabis consumption can result in mental retardation which raises the chances of depression and anxiety. Cannabis is partly responsible for the side effects for example higher

possibility of getting the pulmonary disease and also adverse effects on the genital system in both men and women. Overall, strong marijuana consumption may provide temporary relief from a variety of neurological and psychological manifestations, but extended consumption of high potency marijuana may have serious psychological and physical consequences (Suryadevara et al. 2017).

Small studies have also shown that consumption of cannabis can be a factor in diminishing negative symptoms in schizophrenic patients (Costain 2008; Schofield et al. 2006).

15.14.3 THC Content in Cannabis

Widespread concern about cannabis uses and psychosis was addressed in a study assessing population-induced factors and the occurrence of schizophrenia concluded that the first events of psychosis would be lowered to 12% if increased tetrahydrocannabinol substance was not found (di Forti et al. 2019).

15.14.4 Cognitive Performance

Numerous studies have indicated that patients who suffer from psychosis had improved cognitive function when they consumed cannabis as opposed to non-consumers. This finding is ironic because in healthy individuals, consumption of cannabis results in diminished cognitive functions. A GAP study was carried out to investigate this unexpected finding and it was revealed that first-episode psychosis subjects who smoke marijuana had higher current IQ and premorbid IQ as opposed to non-smoker subjects (Ferraro et al. 2013).

15.14.5 Adherence to Medication and Smoking Cannabis

In a study, the impact of marijuana consumption on the severity of the underlying symptoms and conventional treatment effects was studied in 98 individuals suffering from the first event of schizophrenia spectrum disease and received treatment with long-term injection over 24 months. It was revealed that consumption of cannabis increases the chance of recurrence yet apparently did not diminish the therapeutic response when medication compliance was confirmed in schizophrenia spectrum diseases. Although there was an increased rate of recurrence in cannabis consumers, the altogether response was similar, revealing that patients who relapsed were responsive to the treatment and the whole cohort did not distinguish between consumers and non-consumers (Scheffler et al. 2021).

15.15 Conclusion

Keeping in view all the current evidence, it can be concluded that cannabis does have a role in the occurrence and progression of SZ. It is also known that the use of cannabis reduces negative symptoms and improves cognitive performance. Adolescence is the period when individuals are likely to experience negative effects of marijuana use. Therefore, it is appropriate to develop a preventative program to limit the use of cannabis in adolescence and further research is required to get a deeper understanding of the social, physical, and mental effects of cannabis use to avoid the harmful impact of cannabis use in the community.

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Chapter 16
Medical Imaging and Schizophrenia: A Study on State-of-Art Applications

Akansha Gautam and Indranath Chatterjee

16.1 Medical Imaging System

Medical science is one of the pivotal science branches which deal with the patient's health and their process of healing. Due to the expeditious growth in the medical science field, whole civilization is profited. It is the deep study of how a healthy human body functions. Knowledge of how a human body works is the prerequisite in order to diagnose a disease and restore the healthy body. It is concerned with the research and examination of a human's state of physical and mental health or fitness. The human body is the most complicated in structure. It requires a large amount of effort to make a human body function properly throughout a life. Practitioners take care of patients, and supervise the treatment plan to ease the extremity of a disease. Firstly, correct diagnosis is more important than the treatment. In order to diagnose diseases, medical experts first need to figure out the actual working of a healthy human body. Fortunately, there are now many ways to find what is happening inside a human body using waves like electromagnetic waves and sound waves. Better diagnosis will be provided to people if we have more sophisticated bio-instruments (Ganguly et al. 2010). Medical science is divided into many branches or areas of specialization which includes physiology, anatomy, and pathology with some micro-biology, biochemistry, molecular biology, and genetics. Internet of Things (IoT) might be used to associate all devices which can help in the medical field in hospitals for the assemblage of big data (Serte et al. 2020). Analyzing a large amount of medical data from various locations and census will determine which conditions improve a particular treatment's effectiveness and which do not work (Gautam and Chatterjee 2021). It is very important to not only classify a person with a certain

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disease but also provide a treatment with more preciseness as the interest is growing in personalized medicine, since different treatments may be required for different biological origins of the same disease (Schnack and Hugo 2019).

Medical imaging is the technique and procedure of projecting interior body organs or tissues using different technologies in order to observe, diagnose, or medicate the medical conditions. It provides extensive visualization for every organ present inside a human body. Medical visuals play a very important role in taking the right decision at the right time. Each kind of technology gives distinct information about the area of the human body as per the possible disease, injury, illness, diagnosis, or medical treatment. This technique is very helpful in giving better and more accurate results in modern science. It adds an advantage at each and every stage of a process where it is applied. It is an essential technique in paving a better care path, performs clinical analysis intensely, and allows taking better medical decisions by creating a visual representation. It provides an immense value in constantly enhancing the efficacy of the treatment. Medical imaging system plays a significant role in the research and development field to produce more refined outcomes and treatments. It has the capability to divulge the internal structures veiled under skin and bones. Medical imaging also builds databases of normal anatomy and physiology to make it possible to find out abnormalities. With the help of a medical imaging system, a better clinical diagnosis and therapy is provided to the patients. Automated methods are crucial in order to minutely examine huge amounts of medical imaging data.

16.2 Types of Medical Imaging Techniques

There are various imaging modality techniques used by physicians such as MRI, CT scans, ultrasound, PET, and X-ray which helps them in detecting, diagnosing, and curing severe diseases (Serte et al. 2020). On a broader perspective, it is a part of biological imaging and includes radiology, endoscope, thermograph, medical photography, and microscopy (Ganguly et al. 2010). These techniques are used to provide internal images of the human body for medical applications. It is possible to produce different kinds of images with an ease and different image processing techniques can be applied to these medical images to study carefully and precisely (Azhari et al. 2014). Medical imaging system has grown exponentially over years. There is a tremendous development in the eruption of new medical imaging modalities. Modern medical imaging includes not only image production but also image processing, image recording and storage, computer-aided diagnosis (CAD), and image transmission, most of which are included in the archiving of a picture and communication system (PACS) (Kunio 2006). With the evolution of computer and image technology, the healthcare system has been greatly benefitted (Fig. 16.1).

Medical imaging figures out different disease states that allow doctors to diagnose injuries without intruding. It provides the visual representation that further provides assistance in identifying the root cause of the illness.

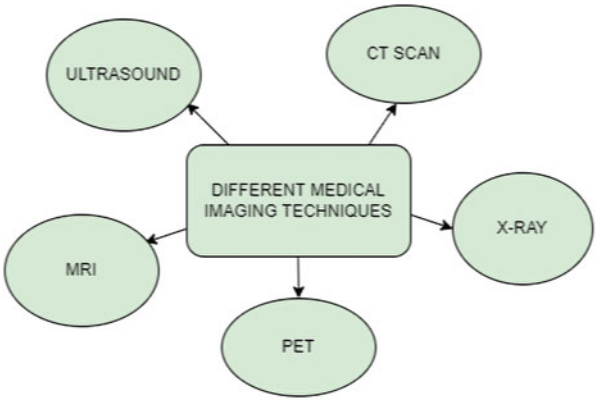

Fig. 16.1 Various Medical Imaging techniques

16.3 Schizophrenia and Medical Imaging

Schizophrenia is a chronic brain disorder which makes the human unable to think, feel, and behave properly. People suffering from schizophrenia have impaired physical health (Nygård et al. 2019). Its symptoms include delusions, disorganized thinking and speech, bizarre behavior, hallucinations, dearth of speech, lack of emotions, flattened affect. Life expectancy is reduced by 15 years of patients suffering from schizophrenia (Sadeghi et al. 2022). Its early signs may include anxiety, depression, trouble concentrating, nervousness, restlessness, low energy level, social withdrawal, unclear thinking, diminished self-confidence, etc. Brain is one of the most important and complex organs of the human body. Entire body is controlled and commanded by the brain only. Many structural and functional changes happen in the brain of a patient due to several chemical alterations. This also leads to improper working of the patient's memory. It interferes with the human's ability to think properly (Fig. 16.2).

Several studies have shown that schizophrenia imposes structural changes in the human brain (Chatterjee et al. 2020a, b). These changes negatively attack a patient's emotional and behavioral capabilities as well as cognitive impairment. In addition, patients who are suffering from schizophrenia disease often manifest a deficiency in working memory which unfavorably impacts the attentiveness and the behavioral characteristics of a person (Chatterjee et al. 2019). Schizophrenia is contemplated as a neurodevelopmental disorder with several external factors playing a role collectively. As per World Health Organization (WHO) data, about 21 million people throughout the world are suffering from this disorder and average age in women is 18 years, and in men, it is 25 years (Sadeghi et al. 2022). Schizophrenia is still one of the great challenges when it comes to diagnosis at the early stage and recently techniques like computer-aided diagnosis based on resting-state fMRI have been emerged to counterfeit this challenge (Algumaei et al. 2022).

Machine learning and structural magnetic resonance imaging are more often being applied to computer-aided diagnosis of diseases associated with brain such

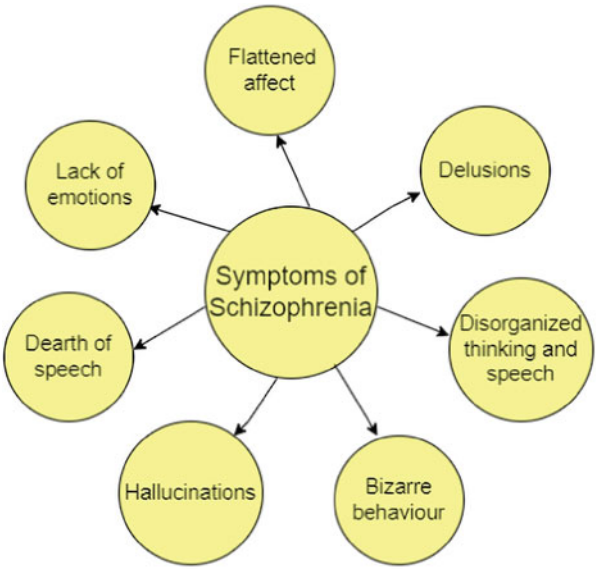

Fig. 16.2 Symptoms of Schizophrenia disorder

as glioma segmentation, schizophrenia, Alzheimer, etc., with the speedy development of booming techniques like artificial intelligence and medical imaging techniques (Yu et al. 2018). It is observed that conventional and deep learning-based methods are prominent enough in the medical imaging sector, as they have potential to contribute to precision medicine and derive different biomarkers like diagnostic, prognostic, and predictive (Bashyam et al. 2020).

To study various brain diseases such as schizophrenia, electroencephalogram (EEG) is remarkably used as it has features like high temporal resolution information, non-invasive in nature, and cost-friendly at the same time (Shalbaf et al. 2020). As per the old studies, it is noticed that there is relationship between sex hormones and cognitive dysfunction in disease like schizophrenia (Song et al. 2020). It was explored that sex hormones act as potential biomarkers in distinguishing initial stage of schizophrenia in patients from healthy person (Song et al. 2020).

16.4 Types of Neuroimaging

Neuroimaging is one of the medical imaging branches that deal with the brain or nervous system and its structural and functional activities. It is considered as a very crucial field of neuroscience. It helps in diagnosing and judging brain health. It not only discovers the actual working or functioning of a brain but also evaluates the different activities that impact a human brain. Neuroimaging provides different ways to study psychiatric disorders. In order to have a better understanding against brain pathologies of patients, qualitative and quantitative both exam results based on well-

formed methods in cross-sectional neuroimaging are being provided by radiologists (Hainc et al. 2017). There are many newer and faster scanners with improved image quality and higher spatial and temporal resolution are included in the field of neuroimaging for better acquisition and analysis (Wintermark et al. 2018). There are different types of neuroimaging technologies which include computed tomography scan (CET), magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), positron emission technology (PET) scan, etc. These technologies allow us to see the internal structure of a brain or to look at the brain activity or function. Neuroscience plays a significant role that helps in diagnosis and evaluation of a disease. Neuroimaging techniques can be divided into different categories such as structural, functional, molecular (refer Fig. 16.3).

CT scan is a type of structural neuroimaging. From various locations, it involves captivating X-ray images around the head. These images then collectively create an image of a brain. Basically, it is an X-ray procedure that constructs cross-sectional images of bones and soft tissues with the help of computer processing. CT scan has more preciseness as compared to conventional X-ray images. In conventional X-ray procedure, there is a fixed tube that emits X-rays only in one direction whereas in CT scan, a motorized X-ray source is used that produces narrow beams of X-rays that rotate around the patient in order to take X-ray images from different angles. Placed opposite to the X-ray source, there is also an X-ray detector which detects the X-rays that are passing through the patient and further transmitted to the computer. Image slices are either displayed in 2D or 3D form that can help in highlighting any abnormalities which will eventually help the physician to plan and provide the treatment to the patient. The resolution of CT scan is relatively low but any major structural abnormalities in the brain such as tumors can be visualized.

Magnetic resonance imaging, or MRI, helps the physician to find, monitor, and treat the medical problems. It involves a combination of magnetic fields and radiofrequency energy waves which are applied to the brain. It is also a structural neuroimaging technology. It uses very strong magnetic radiowaves and a computer to capture the images of the inside of the human body. The magnetic fields and radiofrequency pulses get response by hydrogen atoms by emitting energy. MRI machines use this emitted energy to produce an image. A computer uses that information to redevelop the image of a brain in higher and better resolution than

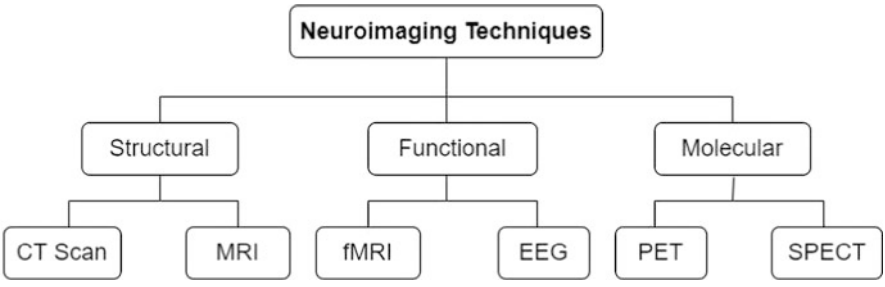

Fig. 16.3 Classification of neuroimaging techniques

CT scan. MRI images are more detailed and refined as compared to other medical imaging methods. Patients are asked to remove all metal objects before MRI procedure. MRI is not considered safe if there are any medical implants such as a pacemaker that a patient may have in your body. MRI scanners are very noisy so patients are asked to wear earplugs or headphones. Technologists operate the scanner from the next room. There are both open and closed types of MRI scanners available but images captured from closed scanners are much precise and better in quality. There is a two-way speaker present inside the scanner for communication. During the entire process, a patient has to be very still in order to get clear images. MRIs are helpful in discovering brain damage, bleeding in the brain, brain changes that happen in stroke, problems with the back, comparing different brains or brain development, and to find out any injury inside a body.

Positron emission technology, or PET scanning, is a way of imaging brain functionalities. It produces 3D images of the body. In PET scan, a radioactive substance is injected into a patient's body that generates positrons which further produce gamma rays when they strike with electrons in tissue of the brain.

PET scanner detects these gamma rays due to the presence of radioactive substances that were injected into the bloodstream of a patient. PET scanner is identifying the blood movement throughout the brain. When the area is active, blood flow around that region of the brain increases. PET scan develops an image of those areas of the brain that are mostly active while the person is going through the scan. The potential of PET scan is very huge. It can help in detecting cancer, testing heart function, and problems like Alzheimer.

Functional magnetic resonance imaging, or fMRI, uses a similar approach to MRI but uses different responses of oxygenated and deoxygenated blood to detect irregularities in the blood flow. In fMRI, the brain is exposed to multiple magnetic fields. Scanner receives electromagnetic signals to generate the high-resolution images of the brain. Blood oxygen-level-dependent method is used to identify the changes in the levels of oxygenated blood in different regions of the brain. It also highlights the areas in the brain which are most active. It is a functional neuroimaging technique. It shows activities of the brain along with high-resolution structural images.

A huge sample is required for investigating the neurobiological bases of psychiatric disorders that have to be understood from an elaborative perspective starting from early stages of the diseases. The magnetic resonance imaging (MRI) is considered as a standard technique to explore the anatomical and functional underpinnings of such illnesses. The magnetic resonance imaging (MRI) is one of the significant neuroimaging techniques used to inspect structural/functional brain deformities in schizophrenia disorder which provides its high spatial resolution (Sadeghi et al. 2021). Functional magnetic resonance imaging (fMRI) plays an important role in designing the automated tools for the identification of schizophrenia (Chatterjee et al. 2020a, b). The rapid advancement in the acquisition and analysis of fMRI data has given us the powerful opportunities to dissect brain functionalities. fMRI has restructured the field of human neuroscience drastically (Table 16.1).

Table 16.1 Different types of neuroimaging techniques

Neuroimaging technique	Image quality	Cost	Advantages	Disadvantage
CT scan	Low	Low	Low cost, high availability	Relative low resolution
Structural magnetic resonance (MRI)	High	High	Low cost, high resolution, and availability provide functional information	Noisy, time consuming, image distortion, cannot be done in presence of any metallic implants
Functional MRI (fMRI)	High	High	Non-invasive and high resolution	Loud acoustic noise, expensive, metallic implants exclusion criteria
Positron emission tomography (PET)	High	Very high	High resolution, good diagnostic accuracy	Very expensive, invasive

16.5 Machine Learning and Deep Learning Techniques

Artificial intelligence is a study of "Intelligent Agents." Artificial intelligence is like a bigger umbrella under which techniques like machine learning and deep learning come together. It is a technique that enables the machine to mimic like humans by replicating the behavior and nature. Machine learning (ML) is a subset of AI that learns data itself with minimum human involvement in order to classify patterns or predict future or uncertain conditions (Kim et al. 2019). It is an application of artificial intelligence that provides systems with the ability to automatically learn and improve from its own experience without any human interference. Machine learning algorithms are designed in a way that they can learn and improve over a period of time when they are exposed to new data. Natural behavior of humans is to learn which has been made a pivotal aspect of the machines as well in today's era (Shinde and Shah 2018). Machine learning is one of the prominent fields in the modern computing world. On the other hand, deep learning is a subfield of machine learning that is concerned with the working and imitation of a human brain. It is influenced by the functionality of human brain cells called neurons. Machine learning enables the machine to make data-driven decisions to carry out a particular task. Artificial intelligence has significantly played an important role in different domains like education, healthcare, entertainment, business, and IT. A machine is called "Artificially Intelligent" only if it is capable of learning and problem solving like a human brain does. As we have plenty of data generated from devices, sensors, and social media users along with more advanced algorithms and high-end computing power and storage capacity, we can easily deal with such amounts of data in order to produce the relevant results (Fig. 16.4).

The deep learning algorithm gets a lot of attention these days as it has a capability to resolve various difficulties in medical imaging fields (Kim et al. 2019). Artificial intelligence is evolving rapidly with its great contribution in observing patients and

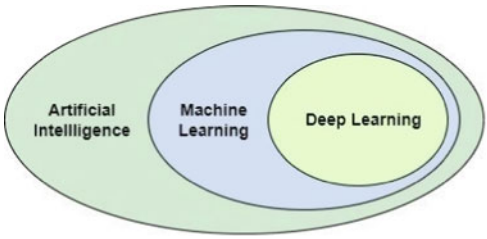

Fig. 16.4 Artificial intelligence, Machine learning, and Deep learning

management control in the health domain. There are many advanced technologies now which are greatly serving different types of operations in the health industry such as prediction of future diseases, data management systems, and examination of patients' health conditions (Salloum et al. 2020). Machine learning is a component of artificial intelligence. With machine learning techniques, a machine or model can learn and improve on its own using the given data access. It helps in increasing the performance of a computer. Deep learning is the next evolution of machine learning.

In order to design operational models of the brain in the field of neuroscience, machine learning came into existence. Nowadays, machine learning is increasingly being applied to medical data, often, neuroimaging data. Machine learning and deep learning approaches can help in analyzing enormous amounts of healthcare data. Neuroscience data are generating at an ever-increasing rate due to various advances in imaging and recording throughput which is developing the need for efficient data analysis approaches (Vogt 2018). Deep learning has the capability to strengthen trainable models from different principles and circuit models which are competent enough to perform complex tasks.

Cognitive neuroscientists can use deep learning in their respective work at different levels of abstraction, from inspiring theories to serving as full computational models (Storrs and Kriegeskorte 2019).

Based on variables in the outside world and long history, neuroscience is able to develop encoding models, which desires to predict neural activity (e.g., spikes in an individual neuron, or BOLD signal in an fMRI voxel) (Glaser et al. 2019). Machine learning would not be required to encode different models if simple methods were precise enough in describing various neural activities (Table 16.2).

16.6 Scope of Future Work

As the new innovations accelerate, development in machine learning, and artificial intelligence technologies are speeding-up, we can expect expeditious changes in the field of medical imaging and healthcare systems. Evolution in new business models and different technologies will help in analyzing medical data on a bigger picture. These technologies will continue to exert a powerful impact in one of the important fields like medicine. It is important to highlight that medical imaging data are increasing exponentially and it will keep on rising. Relevant advancements in the

Table 16.2 Related studies on schizophrenia using neuroimaging

Author	Year	Applied techniques	Dataset
Jilka et al.	2022	Supervised machine learning pipeline, SVM, RF model	Public tweets were extracted between January and May 2018 in real time, Twitter's API via the Tweepy Python library to collect tweets
Lin et al.	2021	Machine learning algorithms including MFNNs, SVM, linear regression, and random forests, M5 prime feature selection algorithm, bagging predictors	China Medical University Hospital and affiliated Taichung Chin-ho hospital in Taiwan
Chand et al.	2020	Novel semi-supervised machine learning methods	PHENOM subsample
Chatterjee et al.	2019	ICA, statistical feature selection, SVM	The SIRP task fMRI data from the FBIRN phase II repository
Jauhar et al.	2018	Unsupervised (hierarchical clustering) and supervised (regularized logistic regression algorithm and nested-cross-validation)	Northwick Park "functional psychosis" trial dataset

field of neuroscience have given researchers and clinicians an opportunity to visualize the human brain and draw different conclusions based on the same. This has led to quantitative assessment of the structure and function of a brain. Along with the clinical evaluations, better machine learning algorithms are required in order to produce accurate diagnosis.

16.7 Challenges of Neuroimaging

Different artificial intelligence technologies along with advanced image processing methods are used to obtain accurate diagnosis for schizophrenia. Despite having many pivotal advantages, there are still some limitations for using neuroimaging technologies. Some of them include its cost of use, which cannot be used with patients wearing metal devices such as pacemakers. It is quite challenging to deal with claustrophobic patients and impatient people who are afraid of going through various neuroimaging techniques. Brain imaging techniques can create a financial and psychological strain on a patient. The outpouring of neuroimaging data collected over a period of time has also led to the "Big data" problem. Different tools and techniques are required to extract the information and analyze it for better decision making. Applying these technologies and bringing it into clinicians practice is also one of the challenges.

16.8 Conclusion

Neuroimaging techniques are valuable tools that can help in analyzing the information and assessing potentially preserved mental processes following severe brain injuries. As the availability of neuroimaging has increased over a period of time, their use by the wider neuroscience community has increased greatly. Neuroimaging has reshaped our sight to examine the neurobiological basis of behavior. These advancements have promised us to offer paramount insights into the working process of the brain of a human being. We look forward to the future of the neuroimaging field which gives assurance to be progressively innovative and integrative towards its approach, increasingly phenomenological, and more admissible to the understanding of complicated human behavior.

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Chapter 17
Schizophrenia and Its Effect on Marital Satisfaction

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17.1 Introduction

Schizophrenia is one of the most serious mental health concerns in the eye of every mental health professional. Besides being a serious mental health concern that requires a good amount of financial backup to avail the treatment processes, it also relates to disruptions in the bonding and connection between the family members, causing a heavy air of uncertainty, discomfort, and distress. It indeed, when developed, affects the person to think, feel, and even behave in a way that the society perceives to be "Not Normal" or simply "Deviant." When the schizophrenic traits are full-blown, the person loses touch with reality. An imaginative world that either becomes a source of underlying fears or a world that would comfort them and sweep them off their feet, avoiding all the real-life events causing a series of acute stress and anxiety. Now, even though the individual who is suffering from schizophrenia goes through turmoil on a regular basis, a part of the deviancy that they showcase is bound to be taken up by the residing family members, friends, or anyone who are close to them. More than anything, if schizophrenia is left untreated, in the long run, the escalation of the severity can become persistent and crippling for both the patient as well as for the family.

When we mention family (after marriage), we also connote the presence of the patient's spouses, in-laws, children, and other immediate family members. Marriage in India is an Institution; you may consider it a social obligation that both the genders have to fulfil, or most individuals decide to get married thinking that cohabitation will make life a little less lonely and yield a good amount of support for mental as well as physical health. The relationship between marriage and mental illness stands to be a lot more complicated than anticipated. The major issues arise during psychotic disorders. Schizophrenia is considered to generally begin in the early,

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middle, and late stages of adulthood since psychotic disorders are typically diagnosed when a person is in their adult phase. The primitive factor that drives the situation when the individual is dealing with mental health issues is that the person is unsure of whether a marriage will be the best option. Among the multitude of pros and cons, what matters is if getting married will help them lead an improved life or rather deteriorate the condition significantly. In India, usually, the choice of spouses is made by the family members or the parents, and if carefully analyzed, there is a pool of other factors that contribute to the decision-making process, and most of them do not align with the variable of "mental illness." The process relies on multiple insignificant or rather significant factors from astrological interpretation, caste regulation, dowry expectations to geographic proximity. Many case studies conducted on people with mental illness like bipolar disorder showed that married individuals had experienced longer episodes of illness. The study also revealed that men are more inclined to be ill than females. Though there was no evidential effect of marriage in patients with bipolar disorder, the effects of marriage on women with schizophrenia concluded that most of the family members mentioned that marriage could resolve or cure the mental illness. In many instances, childbirth was the technique to protect separation in marriage. The severity of the condition also suggested that the adjustment problems heightened, and there are higher chances of antagonistic interaction among the family members (Thara and Srinivasan 1997a, b).

Picking on the definition of marriage, it is a state of being coalesced as spouses in a contractual and accordant relationship by law. However, in India, marriage is considered a union between two individuals, and it is also a union between two families. Even in this era, there is a lingering belief within the community that marriage can lead to fixing an individual's mental illnesses. Mental health professionals are often asked to shed some light and provide advice regarding individuals with any mental health ailments getting or thinking of getting married. Suppose we try to weigh the outcome in one way. In that case, we might see that the emotional support that the individual ought to receive after marriage might improve the physical and mental well-being of both parties. Still, at the same time, marriage can also expose the parties to mental distress if there are problems in adjustment. Thus, evaluating the relation between marriage and mental illness is far from simple. It is a complicated and controversial topic. Many studies also show that individuals with mental illnesses face marital discord, separation, and divorce after tying knots of marriage. The rates are exceedingly high in cases where mental illness is present compared to the general population (Thara and Srinivasan 1997a, b).

Marriage being a social process that requires social abilities to make it a successful venture, it is often seen that schizophrenia reduces or rather curbs the ability of the individual diagnosed with it to have or fulfill these areas, and this might lead to low marital rates, especially in cases of men (Thara and Srinivasan 1997a, b). A paper that dealt with changing marital status in the band of 70–76 patients with onset of schizophrenia followed by an assessment of ten consecutive years showed a fairly high marital rate of nearly 70% in the sample. But the outcome was these marriages either showed men remaining single and the women cladding broken marriages

(Thara and Srinivasan 1997a, b). Since a good marital outcome with the outcome of keeping the marriage intact relies on many sociodemographic variables, a person with illness who faces auditory, visual, and tactile hallucinations deeply affects the quality of marriage and simultaneously affects marital functioning.

The chapter emphasizes on understanding how a mental illness as serious as schizophrenia can affect one's quality of marital life and how marriage can impact an individual with schizophrenia. Through a deep analysis of various literature, we could identify that there are a myriad of factors involved in impacting both of these variables.

The chapter also tries to explore marital satisfaction in individuals with schizophrenia through the perspective of Sternberg's triangular theory of love. The theory discusses relationships through the help of 3 aspects: intimacy, passion, and commitment. Robert Sternberg defined intimacy as "a sense or feelings of connectedness, closeness and boldness in a relationship," he referred to passion as "the drives that leads towards physical attraction, romance, sexual consumption and related phenomena in a relationship," and he described commitment as "one's commitment to maintain love for the other person" (long term) and "the decision that one loves a certain other" (short term). Consummate love is said to have all the three components involved (intimacy, passion, and commitment) (Sternberg 1997).

17.2 Marital Satisfaction

Marital satisfaction encircles the attitude of an individual toward his or her own marital relationship. There are multiple pragmatic implications of the married couples that researchers are still conducting their studies on. Among an array of contributing factors of marital satisfaction there are majorly three fundamental facets that are counted upon. The first one being, the progress of the marriage normally in the relational lifecycle and the fluctuations in the levels of satisfaction. The second facet is enacting the regular routine relational maintenance of behavioral aspects, and the third is the role of conflicts and their patterns that directly relate to marital satisfaction. A systematic review survey that published articles from 2005 to 2015 revealed several scientific databases that explored the association between marital satisfaction and the factors affecting it. It was mentioned that determinants like mental health, emotional health, and stability of the married couple highly dictate a successful marriage and marital satisfaction has an equal amount of influence over the success rates. In this survey, the effective factors on marital satisfaction were seen over Iranian men and women. According to the results that they accumulated it was seen that religious, spiritual, and interpersonal factors like communication, interaction with the spouse, sexual intimacy, and even mental health has a positive impact on the levels of satisfaction that the couple will garner themselves with. Sociodemographic factors like occupation, timeline of the marriage, chronological age, number of offsprings, financial stability, and economic factors were equally emphasized upon (Zaheri et al. 2016).

Currently, if we look upon the levels of achieving marital satisfaction through the perspective of psychological health and mental well-being, studies showcased that psychological health is one of the primitive factors that impact a healthy, stable, and successful marriage. It was seen through systematic researches that disorders and imbalance in the mental health significantly reduce the chances to yield a satisfactory relationship with the spouse (Zaheri et al. 2016).

If we look into the multiple agendas of catering to a marital life that would gather satisfaction, we can count on household duties, finances, intimacy, and family interactions. These belongings to the various social cues have the highest chances of not getting fulfilled by the people or rather spouses if either party has been diagnosed with any sort of psychotic disorders like schizophrenia. Dr. Öngür (year) had explained in his research studies that schizophrenia derails the way individuals interpret the social cues and thus creates a sense of confusion in the partner trying to manifest what actually you desire them to do around the house while cohabiting. In many occasions, counselors give a better insight to the caregiver and the spouse to meet the expectations and be supportive and responsible toward the individual with schizophrenia. Moreover, maneuvering over the financial aspects, maintaining the treatment costs of the patient might become expensive and might make the spouse feel overburdened with expenses. Intimacy is another concern here, schizophrenia in people causes them to have a low libido or diminished sexual interest as they might be prescribed to consume antipsychotic drugs. Interaction or rather interpersonal relationship is the fundamental component here as it lays the ground for building trust, comfort, and connection between two individuals. If this piece of the puzzle is missing, it certainly causes detachments among the couple. Schizophrenia triggers disruption in the thought processes and does not allow the person to comprehend the everyday emotions they go through, which confuses, hurts, or even frightens the spouse or the other family members. Conflicts in these scenarios are inevitable as the behavior the patients show is considered to be disturbing and unacceptable at home and in other settings. These issues gain more leverage if the couple has a child or an offspring. All of these reasons might accumulate and cause marital dissatisfaction among the couple (Zaheri et al. 2016).

17.3 Schizophrenia and Marriage

Schizophrenia may deeply affect the possibility of marriage and the marital outcome for an individual. It is interesting to understand why certain individuals diagnosed with schizophrenia are married while others remain unmarried. Through a deep analysis of different literatures, it was also noted that there are a myriad of factors contributing toward good or poor marital outcomes and it is important that we are able to identify such factors. A research paper, a 10-year follow-up study, has shown that marital outcome in Indian patients diagnosed with schizophrenia is good, with no significant gender differences observed. It was seen that there is a fairly high marital rate; the marital rate was 70% in the sample they had taken. Certain factors

like being married before the onset of illness, a shorter duration of illness at inclusion, the presence of children, and auditory hallucinations at intake were all associated or linked with good marital outcomes. But certain factors like being unemployed and experiencing a drop in socioeconomic level and the presence of self-neglect and flat affect at 10 years were all associated or linked with the poor marital outcome (Thara and Srinivasan 1997a, b). It was also reported that a factor such as a relapsing course of illness was associated or linked with a "never married" stale, and occupational stability seemed to be a factor determining they're getting married after the onset of illness (Thara and Srinivasan 1997a, b). When marital outcomes were considered, it was observed that greater male patients had stable marriages. A study revealed that 69.3% of the total samples, which included 101 patients diagnosed with schizophrenia, were married, while it was seen 30.7% were unmarried. Interestingly, it was also seen that a significantly greater number of patients with schizophrenia who were educated were unmarried. One of the significant factors in unmarried people was the age of onset of illness below 25 years. However, it was reported not to be statistically significant, and it was seen that earlier age of onset of illness was a significant factor that led to poor marital outcome (Desousa et al. 2016). A study that aimed to assess the impact of marriage on the 14-year outcomes and also identify the correlates of marriage among individuals diagnosed with schizophrenia in a rural community revealed that unmarried individuals in the year 1994 had higher rates of homelessness and suicide and a lower rate of survival in the year 2004 and 2008 than those who were married. In the 14-year follow-up, it was found that males were more likely to be unmarried, they are also seen to have a higher level of psychiatric symptoms and a lower rate of full remission of illness, and to report a lower level of work functioning, and lower family economic status and as well as with fewer family members and caregiver. The determinants of being married in 2008 included being married in the year 1994, shorter duration of illness, being female, and lower level of education. Being married is predictive of more favorable 14-year outcomes of individuals diagnosed with schizophrenia in the rural community. The study also reported that marriage could be significant for the enhancement of family-based support and caregiving, as well as for improving the community tenure of individuals diagnosed with schizophrenia; the study also suggested developing programs to enhance the opportunity for individuals diagnosed with schizophrenia to get and stay married (Ran et al. 2017). A study reported that individuals diagnosed with schizophrenia showed reduced marriage rate values compared with other groups (234 people diagnosed with major depression and 84 people diagnosed with bipolar disorder) (Pancheri et al. 1990).

In terms of gender differences amongst individuals with schizophrenia in regards to marriage, it was seen that fewer men got married and more women had broken marriages, particularly if they were childless (Thara and Srinivasan 1997a, b). Another study reported that women are more often married than men at the onset of schizophrenia, indicating that marriage has a protective effect on schizophrenia (Watt and Szulecka 1979). A study reported that Indian women experience and face many problems, especially in relation to things like marriage, pregnancy, childbirth,

and menopause. Most studies have indicated that women have better premorbid functioning and social adjustment than men. The study addressed a great need to plan for gender-sensitive mental health services targeting the special needs of these women, and women caregivers deserve due attention (Thara and Kamath 2015). The trend among women diagnosed with schizophrenia to marry and reproduce earlier accounts for their higher fertility compared with men and is associated with the time previous to the onset of the mental disorder (Pancheri et al. 1990). Interestingly, it was seen that married males with low per capita income, education levels, and a positive family history of mental illness had more relapses. Most of the separations were seen within 2 years of marriage, and they were seen amongst the female subjects (Behere et al. 2020). Most of these separation amongst the female subjects could be due to domestic violence or abuse; this view has been supported by the research findings of a study which revealed that due to the difficulties of living with a spouse diagnosed with schizophrenia, there is a high risk for domestic violence, abuse, neglect, abandonment, and the abuse of substances in these marriages. The spouse diagnosed with schizophrenia may be exploited and victimized. It is reported that spouses of women diagnosed with schizophrenia may be ill and may need assistance with their problems; they may experience the burden of this illness and need support and instrumental aid; they may not adequately discharge their responsibilities as caregivers and that can lead to them further victimizing their wives who are already made vulnerable by illness. The study suggests that the family requires assistance (Seeman 2012). Marital fertility for people with schizophrenia did not show differences based on gender, but it was seen that the marriage rate increased in women compared to men (Pancheri et al. 1990).

It is also important to understand the impact of schizophrenia on marriages and also vice versa. A study conducted on 30 married couples in which one spouse had been diagnosed with schizophrenia during the marriage revealed that the study supported the view that in cases where a psychosis of the schizophrenia group breaks out in a person during their marriage, problems or issues related to the marital dynamics bear significantly or have a big impact on the person's psychopathological development (Alanen and Kinnunen 1975), while another study reported that marriage has a protective effect on schizophrenia (Watt and Szulecka 1979). It was important to see what roles did factors like "enduring relationships," "separation," and "expectations from marriages" played when it comes to the marital life of an individual with schizophrenia. The individuals with schizophrenia and with enduring relationships show a more favorable prognosis than those individuals with a history of separation, divorce, or loss of partner especially concerning the social and professional skills. The enduring partnership is mostly reported by the patients as satisfactory even after repeated hospitalizations (Hell and Fürer 1987). A study aimed to examine the effect of marriage on clinical outcome, the severity of illness, quality of life, and disability among the married individuals diagnosed with schizophrenia and to compare the same with never-married individuals diagnosed with schizophrenia. It was revealed that society has a common belief that marriage can cure mental illness. It was reported that most of the subjects who were diagnosed with paranoid schizophrenia had arranged marriages. They partially disclosed their

illness or condition to their in-laws and spouse before their marriage. However, subjects diagnosed with paranoid schizophrenia had lower separation rates than subjects suffering from other types or other kinds of schizophrenia (Behere et al. 2020). Another study conducted in 2009 reported that the participants (involved five married couples with Schizophrenia) had realistic expectations of marriage and identified advantages and obstacles in their marriages concerning their recovery (Yu and Shim 2009).

Schizophrenia is marked by the presence of certain negative symptoms such as anhedonia, social withdrawal, affective flattening which makes the sexual life of an individual with schizophrenia a matter of concern. A study conducted in 2012 revealed that individuals diagnosed with schizophrenia showed lower satisfaction with their marriage as well as with their sexual lives when compared to the controls. It was reported that marital satisfaction of individuals diagnosed with schizophrenia is influenced by factors like violence from spouse; meanwhile, their sexual satisfaction was impacted by factors like age, violence from spouse, conversation frequency after sexual relations, and revealing psychiatric history to spouse before marriage. It was seen that there was a significant relationship between marital and sexual satisfaction amongst both groups (Kang et al. 2012). A study aimed to understand sexual dysfunction amongst women diagnosed with schizophrenia. The study revealed that among the 63 women who were assessed, 44 (70%) reported sexual dysfunction. However, impairment in desire was reported by all women, impairment in arousal by 58 (92.1%), poor lubrication by 30 (47.6%), poor satisfaction by 44 (69.8%), impaired orgasm by 48 (76.2%), and pain by 23 (36.5%). Factors like poor marital quality, higher scores on general psychopathology of the Positive and Negative Symptoms Scale of Schizophrenia, and side effects such as weight gain, disturbance in menstruation, galactorrhea, and dry vagina were significantly associated or linked with female sexual dysfunction in univariate analysis. However, through multivariate analysis, marital quality was alone found to be significantly related to female sexual dysfunction (Simiyon et al. 2016). A study reported that spouses of individuals diagnosed with schizophrenia have poorer marital adjustment and sexual satisfaction when compared to the spouses of individuals diagnosed with recurrent depressive disorder (Aggarwal et al. 2021). A study revealed that individuals diagnosed with Schizophrenia reported poor marital adjustment (in the consensus and satisfaction domains of DAS) and poor marriage quality when compared to individuals diagnosed with depressive disorder. The individuals diagnosed with schizophrenia reported significantly lower sexual satisfaction when compared to individuals with depressive disorder. Interestingly, it was seen that there was no difference in regards to the prevalence of sexual dysfunction between the groups. It was revealed that poor marital adjustment in individuals diagnosed with schizophrenia was associated or linked with lower sexual satisfaction but not with sexual dysfunction (Aggarwal et al. 2019). Such sexual unsatisfaction can also lead to difficulties in conceiving or in diminished fertility rate. Likewise, a study reported that individuals diagnosed with schizophrenia showed reduced fertility and marriage rate values compared with other groups (234 people diagnosed with major depression and 84 people diagnosed with bipolar disorder). The observed decreased

fertility in people diagnosed with schizophrenia indicates their inability to start and keep stable affective bonds (Pancheri et al. 1990).

Acknowledging that schizophrenia affects the interpersonal relationships that an individual has with others is a story half told. Schizophrenia often takes a toll on a parent–child relationship; it is important to understand the state of these relationships. The authors of a study explored that in these marriages (involves individuals diagnosed with schizophrenia), the children were susceptible to a range of potentially pathogenic factors, such as separations, disturbed parent–child relationships, unempathic attitudes, and poor models for reality testing (Alanen and Kinnunen 1975). Another study reported that having a child was a protective factor for separation (Behere et al. 2020).

A caregiver's role is of utmost importance, but it is also important to acknowledge their needs and burnouts. It is imperative that we understand how caregivers cope with such difficult situations and what their experience is as a caregiver. A study conducted in 2002 aimed to understand the burden and the coping strategies of the caregivers of individuals with schizophrenia; the study reported that spouses reported greater emotional burden. Certain significant predictors of caregiver burden were patient′s age, educational level, and level of functioning and caregiver′s use of denial as a coping strategy (Rammohan et al. 2002). It was seen that parents used denial as a coping strategy and spouses utilized negative distraction strategies. A study conducted in the year 2019 aimed to understand caregiving experiences and marital adjustment in spouses of individuals diagnosed with schizophrenia. The study reported that factors like social support and maturity gained with age were important correlates of positive caregiving and dyadic adjustment, which might result in better patient management and outcome. However, factors like excessive burden on spouses in the form of excessive symptoms, relapses, and poor compliance are associated or linked with negative appraisal (Sinha et al. 2019).

17.4 Schizophrenia and Intimacy

Intimacy is defined as "a sense or feelings of connectedness, closeness and boldness in a relationship" (Sternberg 1997). The topic of intimacy has been deeply studied in relation to any individual diagnosed with schizophrenia. A research that was conducted in the year of 2007 interviewed people with Schizophrenia concerning their subjective sense of their own sexuality. The findings of the research suggested that individuals who are diagnosed with schizophrenia merge sexuality into their sense of self. Although schizophrenia affects the various aspects of their sexual lives, many participants were able to establish and maintain meaningful intimate relationships and also form their own definitions and personal meanings of sexuality (Volman and Landeen 2007). Contrary to the last paper, a study was conducted in which 30 partners with chronic schizophrenia were compared to 20 normative partners for three facets of couple relations which are intimacy, passion, and commitment. The participants were instructed to rate these three facets both in

terms of their actual relationship and in terms of an ideal relationship. The authors reported that the research cohort (30 participants with Schizophrenia) revealed statistically significant lower grades of intimacy compared to the control cohort (20 participants who did not have any history of Psychiatric illness) both in terms of actual and in terms of the ideal relationships (Doron et al. 2014). In a study regarding individuals with early psychosis, it was revealed that participants with early psychosis who are single and single students had more negative perceptions of their abilities regarding intimacy and fewer intimacy behaviors than participants who are involved in a relationship (Pillay et al. 2016).

In terms of personality traits, it was interestingly noted that participants (individuals with schizophrenia or schizoaffective disorder) with greater capacities for intimacy had higher levels of openness, agreeableness, and conscientiousness and lesser levels of neuroticism (Lysaker and Davis 2004).

The development of intimacy within the family especially in a parent–child relationship is worth exploring. It is also interesting to see how these children develop intimacy skills and how they view intimacy. A study which focused on understanding adult attachment in children who were raised by parents with schizophrenia revealed a variety of attachment problems, which leads to difficulties in forming secure adult relationships. Issues with intimacy and trust were revealed to be common (Duncan and Browning 2009). A meta-analysis on family adaptability and cohesion in schizophrenia patients revealed that the level of family intimacy and adaptability of individuals with schizophrenia are low (Xu et al. 2019). A study conducted in the year of 2021 aimed to assess the association between childhood sexual abuse and sexuality and intimacy needs over time in adults with psychosis spectrum disorders. The study revealed that at baseline, sexuality (26%) and intimacy (40%) needs were prevalent and shockingly it was seen that 90% of these needs remained unmet or unfulfilled (de Jager et al. 2021).

There are several factors that lead to the development or decline of intimacy. Such factors need to be identified. A study which aimed to explore the gender differences in premorbid social adjustment and intimacy motivation in individuals diagnosed with schizophrenia reported that males with good premorbid adjustment had higher intimacy motivation compared to those with poorer, whereas females with good premorbid adjustment had lower intimacy motivation than females with poor premorbid adjustment (Hien et al. 1998). A study of 2013 aimed to assess the relationship between internalization of stigma, self-esteem, and the ability of individuals with schizophrenia to develop intimate attachments with loved ones. The study stated that the internalization of *social stigma* was a statistically significant core factor that affects self-esteem and the ability to form intimacy among individuals with schizophrenia. Additionally, the study advised that when individuals with schizophrenia start their treatment, it is important to evaluate the level of self-esteem around the early stages of treatment, in order to determine or predict the patient's capacity for intimacy (Segalovich et al. 2013). A literature review aimed to explore the qualitative literature that was regarding sexuality and intimacy issues experienced by individuals with schizophrenia and related psychotic disorders published between the year 2006 and 2016. Around 56 articles were included in this literature

review. Several themes were discussed in the review, in the theme of sexual needs, satisfaction, and desires, the studies stated that sexuality and intimacy as unsatisfactory among individuals who are diagnosed with psychosis. In the theme of sexual dysfunctions, it was stated that the researches which address intimacy and sexuality issues show that sexual dysfunctioning due to psychotropic side effects is perhaps the most studied topic. In the theme of stigma and social functioning and intimacy and relationships, it was stated that some studies report that about a quarter of the people who are diagnosed with psychosis are faced with negative discrimination and prejudice in relation to sexual and intimate relationships. Self-stigma, the internalization of prejudice, can result in social withdrawal and also feelings of worthlessness in relation to sexuality and intimacy. The increase in social isolation and feelings of sexual worthlessness reduces social functioning and opportunities for sexual and intimate participation. This feature might be stronger for individuals living in the community than inpatients. For many individuals, the fear of rejection is a reason to avoid self-disclosure (disclosure of psychiatric vulnerabilities) or even sexual or intimate relationships at all. The literature review also suggests that practice and research that pays attention to the psychosocial aspects of sexuality is highly required in order to develop strategies to address or to acknowledge the often reported unmet needs in the domains of intimacy and sexuality among individuals with psychosis (de Jager and McCann 2017).

Sexual dysfunction is very commonly seen in individuals with schizophrenia. In the year 2005, a research reported that sexual dysfunction is commonly seen in men with schizophrenia who are treated with medications such as olanzapine, risperidone, quetiapine, or haloperidol and is associated with reduced quality of life, diminished occurrence of romantic relationships, and decreased intimacy when relationships are established (Olfson et al. 2005). A study on sexual dysfunctions in schizophrenia revealed that women interviewees felt shy and hesitant to discuss about sexual dysfunction and matters related to intimacy (Tharoor et al. 2015). Contrary to the previous study, a study reported that in spite of mental health professionals' reluctance or hesitation to initiate conversations about sexuality and intimacy with service-users, people with psychosis and their support networks have reflected their desire for professionals to address intimate topics (Southall and Combes 2020). A study published in the year of 2017 aimed to explore which problems people diagnosed with psychosis encounter in establishing intimacy and maintaining intimate relationships. Five comprehensive categories emerged in relation to problems in establishing and maintaining intimate relationships: side effects of medication, stigma and self-stigma, mental symptoms, sexual abuse, and lack of social skills and experience. In the category of side effects of medication and mental symptoms, it was reported that if the interviewees had a partner, the symptoms of psychotic disorder such as social withdrawal, flattened affect, and delusions influenced or impacted their perception of intimacy. Additionally, it was reported that having a partner who knows or understands what it is like to have a mental disorder resulted in higher responsibility and perceived responsibility on both ends, which increased the intimacy amongst partners. But, for some, the exact opposite was true. If both partners are struggling, both might end up taking up too much space

in the relationship, compromising each other's existence as a partner. As a consequence, an elevated level of self-disclosure, both voluntary and involuntary in nature, secondary to symptoms, appeared to result in a reduction in perceived responsivity, at the same time decreasing equivalency and intimacy. In the category of (self-) stigma, a male interviewee reported that both friendly and intimate relationships were brought to an end by others after the man disclosed his psychiatric background. In the category of social skills and deficits, around eight interviewees which makes 29% of the sample viewed their insufficiency of experience in dating as a barrier in engaging in intimate relationships (de Jager et al. 2017).

There is a need for understanding how intimacy may affect the quality of different facets of an individual's life. A study that aimed to assess how sociodemographic and clinical traits, as well as patients' satisfaction with social support, relate to their quality of life, it was revealed that variables like intimacy and satisfaction with friends were independently related to the WHOQOL-Bref total score which indicated the greater the intimacy and satisfaction with friends, the higher the quality of life. In summary, quality of life is influenced by factors like satisfaction with social support, in that if the satisfaction with friends is greater and the greater the intimacy, the greater the quality of life (Guedes de Pinho et al. 2018). A research conducted in the year of 2019 aimed to explore the relationship between quality of everyday social experiences and emotion in individuals with and without schizophrenia, the research reported that the extent to which a participant felt close to the person they were interacting within a given Ecological Momentary Assessment signal was significantly related to more happiness during social interactions across participants (which included individuals with schizophrenia and individuals without schizophrenia), but it was seen that this relationship only remained significant in the HC group (individuals without schizophrenia; healthy controls). It was seen that intimacy of a relationship was also related to more sadness during social interactions across groups (individuals with schizophrenia; SZ group and individuals without schizophrenia; HC group). However, intimacy of relationship was unrelated or unassociated to anxiety during social interactions (Mote et al. 2019).

Several suggestions and interventions were provided by different authors. A study stated that the authors of the study used interventions such as role-plays, modeling, group exercises, and explicit sex therapy audiovisual material in order to enhance intimacy skills of male patients with recent onset of schizophrenia (Lukoff et al. 1986). An article published in 2000 gave important key points regarding sexuality and quality of life of individuals diagnosed with schizophrenia; the article stated that sexuality, sexual relationships, and sexual functioning are significant quality-of-life issues for individuals with schizophrenia. · The article suggested that importance of sexuality should be indicated in the quality-of-life questionnaires as part of the assessment of the individual's well-being. The article also suggested encouraging psychiatric rehabilitation programs to incorporate sexual education as part of their training, to help patients in addressing their needs in this domain by increasing their knowledge and psychosocial skills in this area. The article advised the physicians working in continuing care clinics to be aware of sexual issues and

inquire about s things such as sexual side effects of medications, sexual activity, and safe sex practices with their patients (Assalian and Raymond Te 2000).

17.5 Schizophrenia and Passion

Passion as "the drives that leads towards physical attraction, romance, sexual consumption and related phenomena in a relationship" (Sternberg 1997). In the year 2014, a study was conducted in which 30 partners with chronic schizophrenia were compared to 20 normative partners for three facets of couple relations which are intimacy, passion, and commitment. The participants were instructed to rate these three facets both in terms of their actual relationship and in terms of an ideal relationship. It was seen that the research cohort (30 participants with schizophrenia) showed statistically significant lower rates of passion than the control cohort (20 participants who did not have any history of Psychiatric illness) in terms of actual relationships. But it was seen that the rate for ideal relationships was also lower, but it was not statistically significant. It is also indicated that perhaps individuals with schizophrenia unconsciously decrease their level of passion in order to decrease their autonomic arousal (Doron et al. 2014). In another research, it was revealed a high level of deficits in all the different facets of sexual functioning such as passion, orgasm, and arousal in men and women who are diagnosed with schizophrenia (Fan et al. 2007).

17.6 Schizophrenia and Commitment

Commitment has been described as "one's commitment to maintain love for the other person" (long term) and "the decision that one loves a certain other" (short term) (Sternberg 1997). A study in the year of 2011 aimed to explore the quantitative and qualitative features of friendship in individuals with schizophrenia and to assess the emotional and behavioral commitment, experiences of stigma, and the impact of illness factors that may affect the making and keeping of friends. It was found that the standard of these friendships was generally good. Emotional commitment to friendship and mistrust were more important than current clinical state in deciding whether or not the participant has friends. The study indicated that around 43% of the sample, which is nearly half the sample, reported a high level of emotional commitment to friendship, but this desire was only accompanied by regularly striving or regular attempts to make friends and overcome social obstacles by 22 participants. Additionally, individuals who had no friends were more likely to report low emotional and behavioral commitment to friendship than those who had friends. It was also seen that men were less likely to describe high emotional commitment to friendship than women (Harley et al. 2011). In the year 2014, a study was conducted in which 30 partners with chronic schizophrenia were

compared to 20 normative partners for three facets of couple relations which are intimacy, passion, and commitment. The participants were instructed to rate these three facets both in terms of their actual relationship and in terms of an ideal relationship. It was seen that the research cohort (30 participants with schizophrenia) showed statistically significant lower grades of commitment than the control cohort (20 participants who did not have any history of Psychiatric illness) both in terms of actual and in terms of ideal relationships (Doron et al. 2014).

17.6.1 Schizophrenic and the Relationship with Their Spouse

Diving deep into the context of the relationship between the people diagnosed with schizophrenia, the spouses not only face the specific issues related to the other half's illness but also face the burdens that they have to bag because of the partnership and the family-specific roles and responsibilities. Viewing from the biological perspective, schizophrenia often indicates evaluation from the spouses end as it can severely affect the life and the relationship, the family, and other social relationships they hold. The chronic effects may deteriorate the living standards and the quality of living and that simultaneously subjects the satisfaction level at stake. Even though relationships with a person with schizophrenia are risky, people who do get involved do tend to maintain the relationship for a long stretch of time, trying to not take it to an extent of separation and breaking down. It has been noticed that the couple is able to maintain a stable relationship only if the impairment of the person is perceived to be in a moderate level or a moderately severe level. The shortcomings are irresistible, but there are few spouses who take up a positive stock toward maintaining a stable relationship with the individual. Another aspect is the frequency of the psychotic episodes. Mutual understanding among the couples is extremely demanded and respect for the person suffering pacifies the process (Jungbauer et al. 2004).

17.6.2 Everyday Life with a Spouse with Schizophrenia

New aspects of burden emerge after an acute psychotic episode has ended. The burdens experienced during illness phases, which are relatively stable, are often less severe than those experienced during other phases, but they can have a long-term negative impact on one's quality of life. Schizophrenia is frequently perceived as a threat that hangs over the patient and his or her family like a sword of Damocles. With anxious worries, the ill person is examined for symptoms that could indicate a psychotic relapse. This situation necessitates a constant state of strain on the spouse's strength. Furthermore, because of the patient's diminished strength, many spouses are forced to take on additional responsibilities in the partnership and family. Frequently, this entails unfamiliar, gender-specific tasks that the patient was responsible for prior to his or her illness. An individual whose wife was a schizophrenic

mentioned, “Well, I had no choice but to play the male part. The apartment was renovated by us. All of this was done by me—well, I repaired the wall and did everything else. He stood there and watched me; he didn’t want to do it and didn’t want to do all of this work. I had to re-acclimate to family life and learn to manage everything on my own. We have a garden, and I had to take care of it all by myself. I needed to inquire about the car, and he was simply uninterested.” (Jungbauer et al. 2004).

Because of persistent negative symptoms and/or unwanted side effects of the medication, the patient is frequently perceived as permanently altered and impaired. Showing empathy for the sick person’s diminished strength and changing needs often leads to the subject reducing his or her own needs, such as mutual activities. For their spouses, the passive, uneventful everyday life that many schizophrenia patients find pleasant or appropriate can be very taxing. When the spouse believes that spending at least part of everyday life and leisure time together is important, balancing the different needs is difficult. Time spent at home with the patient often means missing out on joint activities (e.g., going for walks, visiting friends, and going to the movies); daily life in the partnership is perceived as dreary, tiring, and, in the long run, hindering. Another common source of stress in everyday life is the increased likelihood of marital conflict. Following the onset of the illness, some spouses perceive their sick partners to be moody and withdrawn, while others perceive them to be moaning and irritable, or even vicious and aggressive. Subliminal tensions and tense disagreements are reported by study participants, as are fierce verbal arguments, severe threats, and even violence against people and property. Dramatic escalation of conflict can occur, especially when the ill spouse has a proclivity for aggressive and provocative behavior (Jungbauer et al. 2004).

Schizophrenia can permanently ruin joint sexuality, for example, if the ill person’s sexual interest and pleasure are suppressed by the medication’s negative side effects. In other cases, long-term neuroleptic drug treatment causes significant weight gain, which can make the patient feel ugly or unattractive; likewise, the spouse may perceive the patient’s weight gain as a loss of physical attraction. When there is frequent discord, tensions, and dissatisfaction in the marital environment, sexual disturbances can increase. Emotional alienation between spouses can result from constant conflicts and stifled communication. In some cases, the couple chooses not to engage in sexual activity. Several participants in the study report a gradual loss of social contacts, such as when friends and acquaintances distance themselves from the patient and his or her family. In other cases, patients do not put forth much effort to maintain contact because they are afraid of prejudice or lack of understanding from strangers. If a mutual circle of friends and acquaintances existed before the onset of schizophrenia, spouses are particularly affected by the loss of social contacts (Jungbauer et al. 2004).

Subjects who were ill themselves described both the disadvantages and benefits of living with the patient. Mutual understanding and mutual support—two characteristics based on the spouse’s own experiences with a mental illness—are important in everyday life. Certain preferences and needs are frequently shared, such as the desire for a quiet, undemanding routine for both spouses. In some cases, nearly all of

daily life is spent together, resulting in a quasi-"symbiotic" relationship in which the spouses are inextricably linked to one another and have few social contacts outside of the marriage. "I have to show consideration for my wife, she has the same thing I have—Schizophrenia, " says the narrator. I've noticed that she can't take too much at times. She is easily exhausted. [Interviewer: Could you tell me about your day-to-day activities?] We don't do much, to be sure. In our spare time, we rest a lot—how it is we unwind. "We then read a lot, listen to the radio, and watch television. [Interviewer: That does sound like a very peaceful existence.] Yes, it was quiet. We live in a very quiet environment. That's very important to us, I'd say, because we're not easily distressed." (Interview 121; husband of a schizophrenia patient, himself afflicted with the illness) (Jungbauer et al. 2004).

17.6.3 Schizophrenics and Their Relationship with Their Children or Offsprings

In a study conducted, over a sample of a group of 45 adults with one parent diagnosed with schizophrenia. The Connor–Davidson Resilience Scale, a sociodemographic datasheet, and a semi-structured interview schedule were used to assess the subjects. The results revealed that negative social (49%) and emotional (40%) experiences, lack of support from the ill parent (40%), and burden (66%) in various areas were among the experiences they perceived as different from children of healthy parents. The majority of the children were pleased with the parenting they received (70%). Around 60% of them said they had medium resilience, while 24% and 15% said they had high and low resilience, respectively. The majority of those with medium and high resilience had supportive relationships with other members of their family. The most frequently mentioned factor that assisted them in coping with difficulties was social support. In several areas of life, the impact of parental illness has an impact on the offspring. They are more likely to have social deficits such as emotional instability, aggressiveness, and social isolation, as well as struggle with issues such as low self-esteem and social adjustment at work and in marriage. They have negative childhood experiences such as child abuse, neglect, isolation, and guilt. According to studies, they felt hatred for their mother's illness, and for themselves, and they reported poor parenting, excessive caregiving for the mentally ill parent, stigma, and a lack of support from others (Herbert et al. 2013).

Early investigators, similar to those studying vulnerability factors, were interested in determining what factors influence invulnerability among the disadvantaged, paving the way for resilience research. Resilience is defined as a diverse set of behavioral characteristics. It refers to a way of thinking, perceiving, and making decisions in various situations that have clearly defined patterns of thought, perception, and decision-making methods. These aid in surviving a threatening and difficult situation, resulting in a positive outcome despite significant demands, costs, tension, or risk. As research progressed, it became clear that people respond to different

situations with varying degrees of resilience and vulnerability, and protective factors refer to the specific characteristics and/or situations that contributed to resilience. Bonanno's research with adults who have suffered personal loss as a result of bereavement or trauma suggests that resilience is not an inborn trait, but rather one that is forged through many adversities. Hardiness, self-enhancement, repressive coping, positive emotion, and humor are among the traits he identifies. The majority of the resilience research has focused on children, with "good results" being referred to despite serious threats to the child's development. In a study of children born into poverty, Werner and Smith discovered that protective factors such as a strong personal relationship, a pleasant temperament, a large number of friends and interests, and better language and reasoning skills all played a role in resilience (Herbert et al. 2013).

Several studies have determined the risk status of offspring of parents with mental illness, but few have looked at their psychosocial outcomes as adults. Because parental schizophrenia can have a significant impact on children and is a form of chronic stress, it is critical to research the experiences of those who have lived with such parents throughout their childhood. It is also crucial to comprehend the factors that enabled them to persevere in the face of adversity. This will aid in the development of interventions to help people who are facing adversity become more resilient. As a result, the study's goals were to better understand the experiences of offspring of parents with Schizophrenia, as well as their resilience. A large percentage of offspring (80%) were functioning well, which is why they were able to bring their parents with them. The fact that the majority of the parents had supportive relationships among themselves highlights the fact that family support is available for schizophrenia patients. Given that the majority of the patients were women, it is understandable that the husbands were supportive of their wives. Mothers had the illness again in those parents who were separated, and offspring reported fathers being irresponsible or unsupportive in such cases. The findings point to the fact that good relationships between parents and their children appear to be reflected in their relationships with their children. Illness was frequently a factor in parent-child conflict. Growing up with a mentally ill parent was associated with negative social experiences (49%), such as going out with parents or having guests visit them, and not being able to bring friends to their house. Due to the interference of illness, such as suspicion and anger, some of them had broken their relationships with neighbors and relatives. Growing up with a parent who suffers from mental illness brought with it a lot of stigma. The stigma manifested itself in the form of embarrassment in public places, ridicule from others, and the fear that others would mistake them for mentally ill. The majority of the time, concealment was used to avoid being stigmatized. Other studies have found that feelings of stigma are common among family members who live with someone who has a mental illness (Herbert et al. 2013).

The vivid memories of childhood in relation to the parents frequently included memories of the parent's aggressive behavior, experiences of stigma, difficulties in studies, and feelings of sadness as a result of all of these factors. The findings shed light on the severity of the emotional difficulties these children faced. Foster et al. report similar experiences in their study. Fearfulness of the parent's symptoms,

loneliness, and a lack of sense of peace and happiness were among the emotional difficulties encountered. They naturally felt a lack of emotional support as a result of the aforementioned factors, and they also did not receive academic guidance. However, few (2%) reported positive experiences such as becoming more independent because they were able to handle things on their own and developed positive relationships as a result of taking and giving help. They believed that their experiences had taught them to be more selfless. Support from family, friends, and relatives was the most important factor in helping them deal with difficulties (49%), followed by positive distraction, reappraisal, religious coping, approaching, and avoidance. The findings emphasize the importance of having a support system in place, which appears to play an important role in the lives of offspring (Herbert et al. 2013).

More than half of the offspring in the sample were found to have a medium level of resilience, while only a small percentage had a low level of resilience. This is supported by studies that show a high percentage of children of people with mental illnesses are resilient. The characteristics of those with medium to high resilience draw attention to a number of factors that contribute to resilience, including familial characteristics such as warmth, cohesion, structure, emotional support, and positive attachment styles, which appear to play a significant role as a protective factor. The findings, on the other hand, appear to emphasize the importance of "cumulative protective factors, " which are a mix of individual coping strategies, good families, and social factors (Herbert et al. 2013).

17.7 Conclusion

Schizophrenia being a disorder certainly takes a toll on the person diagnosed with it and also on the family members associated with that person. If we consider the current chapter, we have delved deep into bringing out the outcomes when the person with schizophrenia has to deal with societal norms and social cues or even maintain relationship with their spouses and children. The chapter has tried to relate the Sternberg's theory of love, the chapter tried to explore the components of intimacy, passion, and commitment to see how the process blooms in these domains. Although the impact of schizophrenia on intimacy is greatly studied and there is an abundance of knowledge available on it, the same cannot be said for the other two components which are passion and commitment. There is a dearth of research when it comes to exploring the impact of schizophrenia on passion and commitment. Most literatures indicated that all the 3 components (intimacy, passion, and commitment) are diminished or of low level in individuals with schizophrenia. This chapter has put a special emphasis to see how the relationship between the spouses changes and how the respective responsibilities that a married couple is endowed with are nurtured. Schizophrenia is frequently perceived as a threat that hangs over the patient and his or her family like a sword of Damocles. With anxious worries, the ill person is examined for symptoms that could indicate a psychotic relapse. This situation necessitates a constant state of strain on the spouse's strength. Furthermore, because

of the patient's diminished strength, many spouses are forced to take on additional responsibilities in the partnership and family. In cases of offspring, it was seen that there is subsequent affect that gets imposed on the child because of the disturbed parent. In several areas of life, the impact of parental illness has an impact on the offspring. They are more likely to have social deficits such as emotional instability, aggressiveness, and social isolation, as well as struggle with issues such as low self-esteem and social adjustment at work and in marriage. They have negative childhood experiences such as child abuse, neglect, isolation, and guilt. According to studies, they felt hatred for their mother's illness and for themselves, and they reported poor parenting, excessive caregiving for the mentally ill parent, stigma, and a lack of support from others. Several studies have determined the risk status of offspring of parents with mental illness, but few have looked at their psychosocial outcomes as adults. Because parental schizophrenia can have a significant impact on children and is a form of chronic stress, it is critical to research the experiences of those who have lived with such parents throughout their childhood. It is also crucial to comprehend the factors that enabled them to persevere in the face of adversity. Support from family, friends, and relatives was the most important factor in helping them deal with difficulties, followed by positive distraction, reappraisal, religious coping, approaching, and avoidance. The findings emphasize the importance of having a support system in place, which appears to play an important role in the lives of offspring.

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Chapter 18
Mortality Rate in Schizophrenia

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18.1 Introduction

Schizophrenia is a psychotic disorder that causes considerable impairment. It can exert an effect on many aspects of life, including individual, familial, societal, intellectual, and other aspects of functioning. It also leads to delusion, hallucinations, negative thinking/behavior, and slowing of movements/posture. People with schizophrenia have cognitive impairments like memory, problem-solving, and concentration. It affects 24 million (1 in 300) people (WHO 2022). Individuals suffering from schizophrenia die early than others, the probability is 2–3 times higher. This mortality is often associated with metabolic, cardiovascular, and infectious diseases (Laursen et al. 2014). World Health Organization classified the cumulative risk

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factors of mortality for severe mental illness into three categories mainly Individual, healthcare system, and socioeconomic determinants of health (Liu et al. 2017). Individual factors are gene-specific, family history, the severity of disease, lifestyle, etc. Deficiency of medications, the infrastructure of mental hospitals, and improper financing are health system-related factors and insufficient public policies related to mental health, environmental factors, and social support vulnerabilities are social determinants of health (Tiihonen et al. 2009; WHO 2021).

Schizophrenia is considered as a severe mental disorder because of the high mortality associated with it and it is a global health problem (Liu et al. 2017). During 1926–1941, Odegard studied the mortality pattern among schizophrenia patients admitted to Norwegian mental hospitals. He found that mortality was 3.2 times higher among men and 4.8 times among women during that time period (Odegard 1951). In 1998, Harris & Barraclough also reported high mortality among psychiatry patients, particularly among schizophrenia (Harris and Barraclough 1998). Suicide also contributes to high mortality and a meta-analysis found that patients with schizophrenia have 13-fold high chances of suicidal tendency (Saha et al. 2007).

18.2 Historical Development in Schizophrenia

Though signs and symptoms of schizophrenia were known for centuries, the present-day notion has been developed in the late nineteenth century. Emil Kraepelin devised a categorization system that divided people with serious mental illness, including Symptoms of psychosis, in two different groups: bipolar disorder (formerly known as manic-depressive sickness) and schizophrenia (earlier known as dementia praecox). In those with schizophrenia, the prognosis was generally poorer (including increased mortality) than in people with bipolar illness (Shorter 1997). Because some individuals with schizophrenia recovered fully, Kraepelin's dichotomization was later shown to be false, and outcome measurements as a crucial component of the diagnosis have to be called into doubt (Angst 2002). Another system to classify Kraepelinian dichotomization has been offered as a natural result of these contradictions, particularly in Europe (Kelly and Murray 2000). The developmental theory (Murray et al. 2004) claims that bipolar affective disorder and schizophrenia are linked genetically, while the continuum theory (Varma et al. 1997; Torrey 1999; Möller 2003) presents a spectrum that spans unipolar depression to schizoaffective and bipolar affective disorders, with rising fatality across the spectrum. As per ICD classification, Schizophrenia is an illness characterized by basic and consistent cognitive and perceptual distortions.

18.3 Prevalence

The term prevalence refers to the number of people who are currently living with a specific ailment at or during a given time period. It is estimated that overall less than 1% of people are suffering from schizophrenia. As per the WHO, more than 20 million individuals are suffering from schizophrenia (WHO 2022). National Institute of Mental Health (NIMH) data suggest that 0.25–0.64% of the United States population and 0.33–0.75% of the world population suffer from the disease (NIMH 2022). Though the prevalence of the disease is low compared to other diseases, it is frequently associated with health and socio-economic burden. Schizophrenia is among the 15 leading conditions responsible for morbidity, mortality, and disability (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators 2017). Messias et al. (2007) reported that 0.2 per 1000 years are at risk of developing schizophrenia, with a range of 0.11–0.70. The frequency was determined to be around 5 per 1000 years in the same research (Messias et al. 2007). When compared to other chronic mental and physical health illnesses, the financial costs of schizophrenia are disproportionately high, reflecting both "direct" as well as "indirect" costs of productivity lost, participation in criminal justice, demands for various social services, and other nonhealthcare issues (Desai et al. 2013). Saha et al. (2005) identified a lifetime morbidity risk of 7.2 per thousand people, with quantiles of 3.1 for tenth and 27.1 for 90th percentiles, respectively. However, as the tenth and 90th quantiles indicate, the lifetime risk differed significantly between the studies (Saha et al. 2005). Overall, the disease burden of schizophrenia differs dramatically not just between various segments within a community, but also between nations.

18.4 Mortality in Schizophrenia

18.4.1 How to Measure Mortality in Schizophrenia?

Mortality rate ratios (MRRs) have typically been used to describe the extra mortality in people with schizophrenia. The MRR is calculated by a formula in which the overall death rate in individuals with schizophrenia as the numerator and the mortality rate in a reference group as a denominator. The standardized mortality rate (SMR) is determined by dividing the death rate in the schizophrenia group by the overall population death rate, is a notion that is very similar to the MRR. MRR (or SMR) has been demonstrated to diminish with age in people with schizophrenia and the general population. This characteristic, known as "effect modification by age, " is critical to consider when computing MRRs. The fact that mortality among normal individuals is fairly low in the lower age groups explains the impact modification by age. Because MRRs drop with age, it is critical to compare groups with similar age distributions when assessing data. To compare the MRRs of different groups or nations is difficult if the age of a particular group is not recorded,

and the findings may be skewed. Uneven identification of deaths in the two groups is another flaw in MRR calculations. If a country's overall mortality rate is utilized in one group, it is critical to include all fatalities inside the group with schizophrenia to avoid underestimating MRRs. Another technique to quantify higher fatalities among people with schizophrenia is to analyze the deviations in years of life they live compared to those in the normal community. If an individual die at the age of 55, and the population's average death age is 75, a total of 20 years is lost. MRRs have various benefits over excess mortality, which is computed as a change in the years of life lived by persons with schizophrenia compared to the others. The technique takes into consideration the influence of relatively biggest killers with little deaths, and gives earlier deaths greater weight (these are more frequent among individuals with serious mental illness than the regular populace), and provides a simple tool of excess mortality burden. The majority of mortality studies that use record linking to determine expected lifespan rely on it. Individuals with schizophrenia are identified through documented encounters with mental health facilities, which are subsequently linked to death records. In general, researchers use two techniques to determine how long persons with schizophrenia live relative to the normal individuals. The first technique involves calculating life expectancy based on death rates in various age groups. The mortality rate for all age groups is computed using this approach. The second technique determines the average age at which people in the group died using just information on those who deceased.

18.4.2 Why Excess Mortality in Schizophrenia

Main reasons identified by Laursen associated with high mortality in schizophrenia are as follows (Fig. 18.1) (Laursen et al. 2012):

- Physical ailments are frequent, but they are often misdiagnosed and undertreated.
- Antipsychotic medication has the potential to have harmful side effects.
- Unhealthy lives (bad dietary habit, smoking of cigarettes, excess consumption of alcohol, and lack of physical exercise).
- Suicidal tendency and vehicle accidents are more common among schizophrenic patients.

18.5 Health Care and Physical Fitness

In schizophrenia patients, the Charlson Comorbidity Index is commonly preferred to assess somatic comorbidity. This index covers 19 severe chronic illnesses, each with a weighted score based on their severity. A high Charlson index suggests upper side of somatic comorbidity and hence lower side of somatic health. In all but one of the Charlson index's somatic problems, a Danish research found an increased

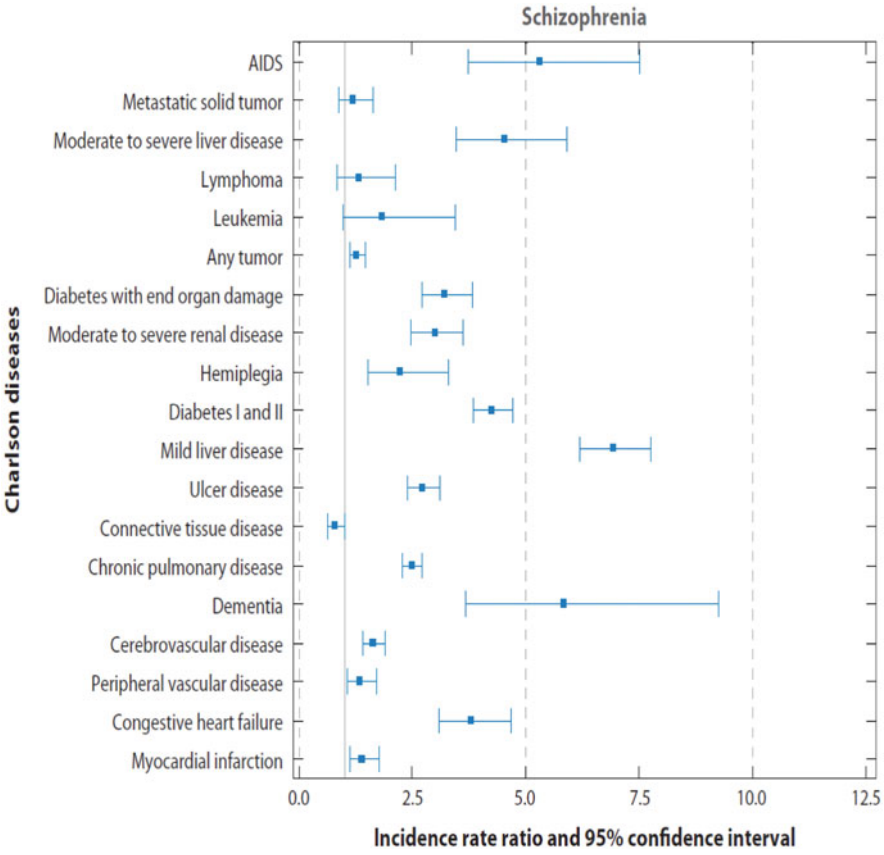

Fig. 18.1 The Charlson Comorbidity Index includes 19 somatic chronic illnesses. The reference is a solid vertical line crossing at 1.0, which covers all people who have never been committed to a mental facility. (Adapted from Excess early mortality in Schizophrenia from Laursen et al. 2014)

prevalence in people with schizophrenia (Laursen and Nordentoft 2011). The Charlson index is twice greater in people with schizophrenia than normal people, suggesting that these people have a higher rate of somatic problems.

18.6 Antipsychotic Medicine Side Effects

Weight increment, dyslipidemia, uncontrolled sugar, and other heart-related risk factors have been linked to antipsychotics, particularly atypical antipsychotics (Newcomer 2007). Antipsychotic medicines have been linked to an increase in fatality among patients with schizophrenia, notably after the release of second-generation antipsychotic medications in the late 1990s (Saha et al. 2007).

Antipsychotic medications raised the incidence of metabolic syndrome, sudden death due to cardiac arrest, and heart muscle injuries (Raedler 2010). However, there was no indication that this risk changed depending on the antipsychotic medicine. Antipsychotic medicine can have undesirable side effects that impact mortality; however, it is not clear that how various antipsychotic molecules alter increased mortality. The effects of two drugs namely ziprasidone and olanzapine, were studied in a randomized study with 18,154 patients of schizophrenia. After 1 year, this study reports that there were no differences in fatality rates across the different groups (Strom et al. 2011).

18.7 Lifestyle Risk Factors

Smoking, physical fitness, food, and weight are all lifestyle variables that contribute to younger patient's death with schizophrenia. Cigarette smoking is one of the leading risk factors that is most likely to contribute significantly to a low life span. Patients of schizophrenia smoke more cigarettes than others. Several researches have looked at the characteristics that influence smoking cessation success in patients of schizophrenia, and research suggests that two drugs namely varenicline and bupropion can help people to quit cigarette smoking. Programs for cessation of smoking and nicotine gum replacement appear to help persons with schizophrenia quit smoking. Bupropion enhanced the likelihood of stopping smoking by 2.8 times (95% CI: 1.02–7.58), according to a Cochrane review, which collected that data from 11 studies, and incorporated 685 patients of schizophrenia who had a habit of smoking daily (Tsoi et al. 2013). The impact of exercise treatment on physical fitness was studied in several randomized trials with 103 patients (VO2 max) (Skrinar et al. 2005; Beebe et al. 2005; Scheewe et al. 2012). All concluded weak association and no further studies conducted afterwards as patients with mental illness are difficult to recruit. Several studies have found that eating choices play a role in weight increase in schizophrenia, although medicine can also induce weight gain on its own. A retrospective analysis was done among 2231 patients with schizophrenia who were recently taken antipsychotic medication for first time using data from the South Carolina Medicaid program. During the first 3 years of therapy, 2.73% of these patients gained weight, resulting in a BMI of 30 or higher (Jerrell et al. 2010). A multinational randomized controlled study of first episode among patients received treatment of several antipsychotic medicines discovered that all antipsychotic treatments were linked to a weight gain of more than 7% during the trial (Kahn et al. 2008).

18.8 Future Initiatives

Till date, no epidemiological study has been conducted to explore the role of these risk factors for accelerating the deaths among schizophrenia. These risk factors not only increase the fatality among schizophrenia, but they also increase the risk of other communicable and noncommunicable disease, which may increase the deaths indirectly. Figure 18.2 highlights the 5-year survival among schizophrenia patients. All these knowledge needs to be implemented through clinical guidelines and policy changes. Though modifiable risk factors can be changed in schizophrenia patients, but there are certain barriers. To improve the life style of a patient, family and professional support play a crucial role as the patient has illness and side effects of drugs. All the patients should be motivated for healthy food and physical activity. The improvement in physical health may also improve the mental health. Nicotine substitution is also effective in stopping the smoking habit.

Though most of the studies identify the risk factors for increased mortality, future studies should also try to explore the sustainability of all these interventions among schizophrenia. The future studies can be done to explore the sustainability of life style modifications and nicotine substitution among schizophrenia patients. Qualitative studies are still to be done to explore the life of a schizophrenia patients and explore the challenges and barriers at individual level.

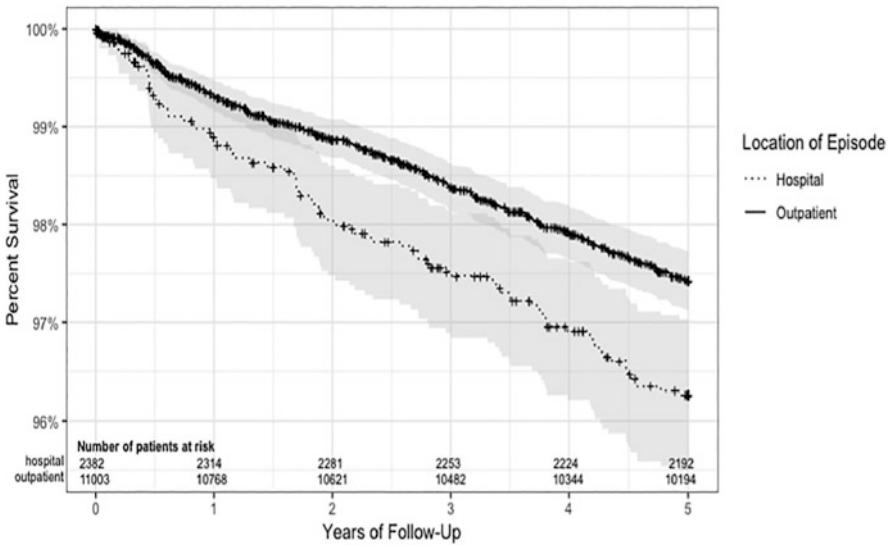

Fig. 18.2 By diagnostic location, 5-year survival (Kaplan Meier curve) after first-episode psychosis among schizophrenic spectrum disorder group. (Adapted from Mortality After the First Diagnosis of Schizophrenia-Spectrum Disorders: A Population-based Retrospective Cohort Study), (Kurdyak et al. 2021)

18.9 Conclusion

Patients with particularly poor outcomes were previously included in the definition of schizophrenia. These individuals have a short life span because of high fatality in all age groups. Patients of schizophrenia not only have a short life span, but they may not have seen the same progress in life span as normal people in recent decades. As a result, the mortality difference not only continues but may also be widening. It is widely established that a higher suicidal tendency in schizophrenia patients correlates to a lower life expectancy. Suicide prevention, particularly in the early stages of sickness, should be a top concern. We cannot continue to ignore persons with schizophrenia's physical health requirements. For this patient population, there are no universal criteria for successful somatic therapy. Possibilities for potentially modifiable factors which contribute to this higher death rate, such as unfavorable treatment effects and lifestyle factors, as well as affordable healthcare for adequate detection and care of physical comorbidity, are the most pressing research priorities.

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