Chapter

Neurobiological Perspective and Personalized Treatment in Schizophrenia

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Abstract

Personalized treatment is the focus of researchers and comes into prominence for both genetic sciences and neurotechnology. Recently, clinical practice tries to follow the idea and principles of personalized medicine. Besides predicting an individual's sensibility or predisposition for developing schizophrenia, pharmacogenetic and pharmacogenomic approaches attempt to define and acknowledge important indicators of clinical response to antipsychotics namely their efficacy and adverse effects. Particularly in the treatment of schizophrenia, clinicians are very helpless in resistant cases, and clinical pharmacogenomics contributes in a revolutionary way. With both phenotyping, namely Therapeutic Drug Monitoring (TDM) and genotyping, "big expectations" emerged both with the right drug, the right dose, and the right time. Both pharmacokinetic genotyping, CYP400 enzyme activity, and pharmacodynamic genotyping could be measured. The chapter handles schizophrenia with neurobiological views and covers personalized treatment approaches from various perspectives. Personalized treatment in the diagnosis and treatment of schizophrenia is presented first. Following comorbid schizophrenia in addition to the use of various substances, psychopharmacology of schizophrenia and the mechanism of action of antipsychotic drugs are presented. Genetics and epigenetics in schizophrenia are studied in detail and *in silico* application and computational approaches covering the feature extraction process and destructive impact of the metaverse are shared lastly.

Keywords: neuromodulation, tTMS, dTMS, pharmacogenetic, psycopharmacology, addiction, drug interactions, therapeutic drug monitoring, personalized medicine, personalized treatment, neuroimaging, deep learning, metaverse, entropy, genetics and epigenetics

1. Introduction

Rapidly evolving MRI technologies and their multimodal combinations provide biological findings that allow support for various hypotheses attempting to explain

schizophrenia. PET and SPECT techniques have been used to study neurotransmitter mechanisms. Magnetic resonance spectroscopy has demonstrated neurochemical changes in vivo in patients with schizophrenia, As a result, we better understand the detailed brain anatomy, pathophysiology, and chemical pathology of schizophrenia. More importantly, findings from neuroimaging studies promise to transform existing diagnostic tools into new functional tools with implications for the treatment of patients. Accumulating data from genome-wide association studies are constantly decoding SZ risk genes. Especially with the widespread use of new generation sequencing systems, it has been shown that more than 200 loci may play a role in the etiology. In addition, epigenetic factors should not be forgotten. Biomarker studies(BDNF,MB-COMT, COMT, RELN and HTR2 etc.) have proven that DNA methylation and histone acetylation are also effective in the development of schizophrenia. The use of epigenetic treatments in practice and the development of gene therapy options provide hope for the treatment of such neuropsychiatric diseases. Targets of psychopharmacology include positive symptoms, negative symptoms, mood symptoms, cognitive deficits, life quality and occupational functionalities. Choice is usually guided by the target symptom and depends on the pharmacotherapy of the drug. Typical and atypical antipsychotic medications are gold standard in the management of the disease. Unfortunately, at the present day there is no obvious or best choice of drug in antipsychotic medication. Several G protein-coupled receptors (GPCRs), mainly dopamine, serotonin and adrenaline receptors are traditional molecular targets for psychopharmacological strategies of schizophrenia. Thus, drug development efforts now target novel important signaling mechanisms of GPCRs. Since the treatment of schizophrenia addresses the phenotype and not the cause, and our current knowledge about the illness is not enough, the pharmacotherapy of schizophrenia is far to yield promising results. There has been a large literature and experience with theoretical neuromodulations such as rTMS, dTMS. With the involvement and applications of artificial intelligence in medical data, patient follow-up strategies and methodologies are likely to happen in the near future. This study focusses on the strategies in this perspective and underline the personalized treatment for the diagnosis and treatment of schizophrenia. Since schizophrenia is in the scope of various disciplines like medicine, pharmacology, biology and natural sciences the chapter is structured and studied with the support of the aforementioned titles of those disciplines.

2. Personalized treatment in the diagnosis and treatment of schizophrenia

In recent years, personalized treatments have come to the fore, both in genetic sciences and developments in neurotechnological discoveries. Especially in the treatment of schizophrenia (SZ), clinicians are very helpless in resistant cases. No new pharmacological agents have been found in the last decade. However, clinical pharmacogenomic developments have revolutionarily come to the rescue. With both phenotyping, Therapeutic Drug Monitoring (TDM) and genotyping, great advantages have emerged in terms of the right drug, the right dose and the right time. Both pharmacokinetic genotyping, CYP400 enzyme activity and pharmacodynamic genotyping, namely Catechol-O-methyltransferase (COMT) and the serotonin transporter (5-HTT) enzyme activity, can be easily measured. On the other hand, a great deal of literature knowledge and experience has been shared regarding

noninvasive neuromodulation treatments with high reliability in treatment, such as repetitive transcranial magnetic stimulation (rTMS) and deep transcranial magnetic stimulation (dTMS). Moreover, it is possible to create patient follow-up systems by combining artificial intelligence and medical records. It is necessary to consider all this information in more detail.

2.1 Phenotyping

TDM is a new method for optimizing drug therapy. The aim is to understand the plasma concentrations of psychoactive drugs and discuss how efficiently they can be applied in psychiatry practice in patient safety and treatment-resistant situations. TDM is based on the principle that there is a close relationship between the plasma level of the drug and its clinical effect. If such a relationship does not exist TDM is of little value. TDM as a preliminary test for genetic polymorphisms;

- Improves therapeutic efficacy,
- Improves drug safety,
- Reduces total therapeutic costs,
- To get results in two days, cheap cost

Psychoactive drugs are divided into four groups for drug blood level monitoring. First, strongly recommended drugs for toxicity monitoring such as lithium, carbamazepine, valproic acid. Second, Follow-up for side-effect control; like clozapine. Third, the ones followed for the anticipation of drug response include drugs that do not want to waste time with trial and testing. And lastly, it is used for the preliminary diagnosis of genetic polymorphism in treatment-resistant cases and for the decision of appropriate drug selection. Genetic Polymorphism can be determined by Genetic Profiling (DNA tests) and is a very valuable parameter for Personalized Medicine. It is very important for the patient's treatment compliance that we can predict the reduced drug effect, increased drug side-effects and toxicity risk. Why is it important to identify genes and proteins related to Gene Polymorphism that might have very important clinical results? Tests for drug efficacy and patient safety are important for the principle of the appropriate drug, dose, and duration. Clinical Pharmacogenetics, which deals with DNA sequence analysis and drug blood level monitoring together, has started an important period in Psychiatry. Knowing the genetic and pharmacological basis of the diversity seen in human response to drugs is no longer a mere scientific curiosity. Follow-up of side effects at the recommended dose, lack of clinical response, and drug interactions have different importance in children and the elderly (see in **Figure 1**) [1].

2.2 Genotyping

In order to predict the possibility of the patient experiencing toxicity, when monitoring medication level increases and decreases are imperative. In order to produce important clinical results, it is important to understand gene polymorphisms. Combining the analysis of psychiatric DNA series and therapeutic drug

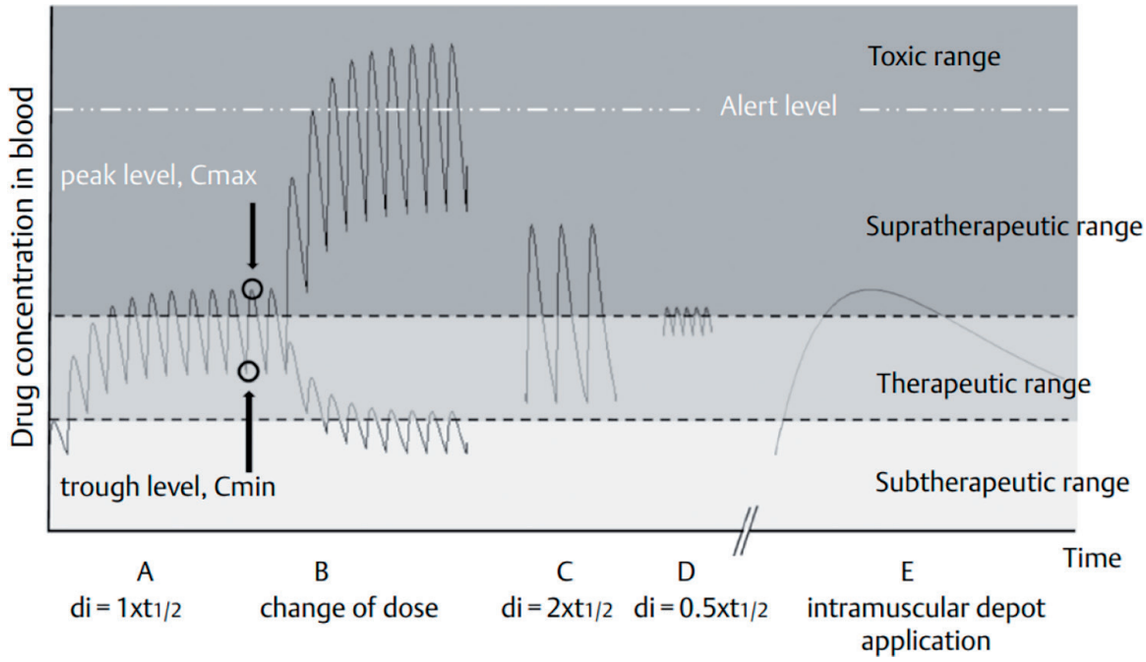

Figure 1.
It is recommended to increase atypical or typical antipsychotics such as clozapine, olanzapine, risperidone, and paliperidone to supratherapeutic level in treatment-resistant SZ cases. Concentration time curve after oral or intramuscular depot medication. A: 94% of steady state (therapy with constant dose) is reached after four elimination half-lives (t1/2) of the drug. At steady-state, drug intake equals drug elimination over a defined time frame. Trough levels at steady state are usually quantified and recommended for TDM. The figure shows a hypothetical drug with a dosing interval (di) equal to its half-life (di = t1/2), a situation found similar for many drugs (e.g., t1/2 = 12 h, di = 12 h, curve A). Trough concentrations are right in the middle of the therapeutic range, i.e., on target, despite the fact that the drug's concentrations during the dosing interval sometimes exceed the therapeutic range. B: Modification of drug concentrations by doubling or halving the dose without change of the dosing interval. C: Doubling the dose interval (di = 2 × t1/2) and administering the entire daily dose once daily results in curve C. The area under the blood concentration versus time curve (AUC) representing the total drug exposition is identical for curves A and C, however, trough concentrations in curve C (24 h after the daily dose) are significantly lower than in curve A (12 h after a half daily dose). High differences between trough and peak levels can be associated with tolerability problems during the phases of high drug concentrations. D: Curve D illustrates the intake of four equal doses per day, resulting in the same daily dose as for curves A to C. Again, the AUC is identical to curves A and C but this time we observe higher trough concentrations. Using this application form, even low doses can be effective, since sufficient drug concentrations are available at the target structures. E: Intramuscular application of depot: Peak concentrations may be achieved after as early as 1 day or as late as 4 weeks depending on the formulation. Concentrations comparable to trough values after oral application can only be obtained immediately prior to the next application. Blood sampling during the elimination phase after full absorption (maximum) will result in higher values compared to trough sampling after oral application despite equal AUC. Please note the time scale for curve E is different from curves A to D [1].

monitoring, clinical pharmacogenomics has started a new era in which patients are provided with a personalized pharmaceutical treatment. So, genotyping findings give us the power of predictability in drug selection based on gene variations (see in **Table 1**).

In **Table 2**, a pharmacogenomic profile is seen regarding which drug to be administered in a genotyping case. Genotyping; works for specific mutations, provides information about metabolic capacity, only one-time oral sampling is enough, results stay valid a life time (Pharmacogenetic ID). Measuring COMT enzyme activity is another genotyping method in order to estimate the effect of antipsychotic drugs on the Pharmacodynamics, namely the Central Nervous System. If COMT enzyme activity is slow, less and delayed response should be expected. Neuromodulation treatment indication and supratherapeutic drug dose should be considered. Measuring COMT

	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4
Substrate	Clozapine	N/A	N/A	Risperidone Haloperidol	Quetiapine
Inhibitor	N/A	N/A	N/A	Haloperidol	N/A

Abbreviations: N/A: Not Applicable, Cytochrome P450 1A2 (CYP1A2).

Table 1.
Example of predictability in drug selection based on gene variations by Tarhan.

Gene	Phenotyping	Enzime activity
CYP1A2	UM	Increased
CYP2C9	UMdim	Decreased
CYP2C19	EM	Normal
CYP2D6	PM	Decreased

Abbreviations: EM: Extensive metabolizer, EM dim: Extensive metabolizer, diminished, PM: Poor Metabolizer, UM: Ultra-rapid metabolizer, Cytochrome P450 1A2 (CYP1A2), Cytochrome P450 family 2 subfamily C member 9 (CYP2C9), Cytochrome P450 subfamily C member 19 (CYP2C19), Cytochrome P450 family 2 subfamily D member 6 (CYP2D6).

Table 2.
Example of genes, phenotyping and enzyme activity by Tarhan.

enzyme activity is another genotyping method in order to estimate the effect of antipsychotic drugs on the Pharmacodynamics, namely the Central Nervous System. If COMT enzyme activity is slow, less and delayed response should be expected. Neuromodulation treatment indication and supratherapeutic drug dose should be considered. COMT is responsible for the O-methylation of catecholamines, chemical compounds derived from the amino acid tyrosine [2]. Although the structural organization of COMT is currently conceptualized as a single gene, this single gene encodes two similar enzymes. One is soluble and is called S-COMT. The other is membrane bound and called MB-COMT. A well-known genetic variation of COMT was described more than 30 years ago [3]. This genetic variation was called as the Val 158Met polymorphism for many years, referring to an amino acid change at position 158th in the amino acid sequence of the membrane-bound form of the enzyme. It is also less commonly referred to as 472G/A. This functional polymorphism has been assigned a unique reference sequence number, rs4680 now. Val allele of rs4680 (guanine allele) is a more active allele than Met allele (adenine allele) and has been accepted as a risk factor for SZ [4–7]. In summary, the introduction of genetic profile monitoring into routine psychiatric practice in TDM and resistant cases, which is a faster and easier method, seems to be a revolutionary development. Certainly, the availability of special tests for personalized treatment has been the greatest contribution of science to the clinic.

3. Comorbid schizophrenia in addiction

Alcohol and substance use disorders (ASUD) is a diagnostic group that has been shown to frequently accompany other mental illnesses in many epidemiological studies [5]. One of these mental illnesses is psychotic disorders, and a well-known

example is SZ. Addiction and SZ are both chronic disorders with serious consequences both at the individual and the public level. Substance use in SZ as "self-medication" is presented as a hypothesis, suggesting that substances are used to control or alleviate the symptoms of SZ. This hypothesis claims to predict the selection of the substance used according to the present symptom. For example, patients with SZ may be expected to use stimulants for their negative symptoms. In reality, stimulant abuse is not common in SZ, and many studies do not support this hypothesis. People with SZ often tend to abuse easily accessible substances. Reasons for use are similar to those of the general population ('to get high', 'to reduce depression', 'to relax'). The symptoms that are most commonly associated with addiction in patients with SZ are depressive symptoms [6]. The brain reward center theory proposed by Green et al. has received much support for explaining the high frequency of substance use disorders seen in patients with SZ. This theory proposes that there is an abnormality in dopamine-mediated responses in the brain to reward stimuli in individuals with a diagnosis of SZ [7]. Based on animal and human studies, this abnormality is thought to occur secondary to front striatal and limbic structure abnormality in the brain reward center [8]. The lifetime prevalence of addiction in the general population is 16%. On the other hand, even when nicotine use is excluded, nearly half of SZ patients are diagnosed with a lifelong substance use disorder. The Epidemiological Field Study reports that 34% of patients with SZ have alcohol use disorder and 28% have a substance use disorder [5]. Data from the National Epidemiological Study of Alcohol and Related Conditions revealed that SZ is associated with an increased risk for reuse, especially when cannabis is involved [9]. When we take nicotine into consideration, comorbidity rates will increase significantly. Exacerbation of psychotic symptoms, relapse and hospitalization, use of emergency services, HIV, HCV, HBV infections, suicidal behavior and homelessness have been associated with an increased risk of substance abuse in patients with a diagnosis of SZ. These patients with dual diagnoses also have a worse prognosis for other concomitant medical problems such as diabetes mellitus. Addiction comorbidity in patients with SZ seems to be associated with violence and criminal behavior. Substance use in patients with SZ is most often not questioned, screened, or diagnosed. Roughly half of SZ patients can be considered to have an addiction-related problem. Asking about current and also lifelong substance use is a part of psychiatric examination, and this subject should be discussed with every SZ patient [10–12]. Substances used among SZ patients are as follows (in order of frequency): nicotine, alcohol, cannabis and cocaine. The frequency of alcohol use disorder is three, and the substance use disorders is five times higher in patients with SZ compared with the general population. Abuse of more than one substance is quite common in this population. Although nicotine use tends to decrease in the general population, it has been observed at constant rates in the SZ population for over 40 years. Patients with SZ use amphetamines, opioids, and sedative-hypnotics less frequently [12].

3.1 Schizophrenia and smoking

21% of the normal population and 72–90% of patients diagnosed with SZ smoke. Smokers with SZ are addicted to more nicotine than the general population, are more commonly diagnosed with medical illnesses, and less frequently seek help to quit smoking. Negative symptoms such as apathy, positive symptoms such as disorganized thinking, and cognitive impairment reduce both the motivation to quit smoking and the compliance to implement smoking cessation strategies. On the other hand,

smoking also negatively affects antipsychotic drug treatments. Smoking increases the efficiency of the Cytochrome P450 1A2 (CYP1A2) microsomal enzyme system, which is involved in the metabolism of some antipsychotics, especially haloperidol, phenothiazines, clozapine and olanzapine. This may explain the need to use antipsychotics at higher doses in smokers with SZ compared to nonsmokers [13–15].

3.2 Schizophrenia and alcohol use

Studies show that 25–45% of patients with SZ use alcohol at a level that fulfills the criteria of alcohol use disorder [16, 17]. It has been reported that patients with SZ who have comorbid alcohol use disorder have more severe symptoms, are hospitalized more frequently, and have worse long-term treatment outcomes [18].

3.3 Schizophrenia and cannabis use

Cannabis use rates in people with SZ vary between %27 and %42, and these rates are higher than those of the general population [18]. In a follow-up study on cannabis use and the development of SZ, a six-fold higher risk of developing SZ was found in those who reported more than fifty times of cannabis use in lifetime [19]. It has been reported that the etiological relationship between cannabis use and SZ spectrum disorder is related to cannabinoid receptors and some genetic polymorphisms. The cannabinoid 1 (CB-1) receptor is associated with a group of neurotransmitter systems that play a role in the etiology of SZ, such as the dopaminergic and glutamatergic systems. Specific differences have been shown in the regional density of CB-1 receptors in the brains of patients who developed psychosis after cannabis use [20]. In another study conducted on adolescents using cannabis, it was determined that having a functional polymorphism in the COMT gene was a moderate risk factor for the onset of psychosis. It has been reported that the risk of developing psychosis with cannabis use is high in individuals carrying the COMT gene Val-158 allele [21].

3.4 Schizophrenia and cocaine use

Studies have reported that between 15% and 50% of SZ patients use cocaine [16, 22]. It has been reported that cocaine can reduce the negative symptoms of SZ and is often used to relieve depression [23]. It is also known that cocaine causes an increase in dopamine concentration at the synaptic junction, thus increasing Dopamine 1 and Dopamine 2 (D1 and D2) receptor activities, and thus may cause psychotic symptoms in users [24].

3.5 Schizophrenia and stimulant use

While clinical experience indicates that amphetamine psychosis can last for a maximum of 3–6 months, there is insufficient evidence that this substance will directly cause SZ. However, if the individual has SZ sensitivity, it can be proposed that amphetamines used in high doses increase the risk of SZ. Results of a Finnish national study found an 8-year cumulative risk of 30% for a diagnosis of a spectrum of SZ in individuals presenting with amphetamine-induced psychosis [25]. It is reported that approximately 26–46% of individuals with methamphetamine addiction have amphetamine-induced psychosis [26]. Symptoms of methamphetamine-related psychosis are similar to those of paranoid SZ. Auditory hallucinations, persecutory

and reference delusions are common. Negative symptoms appear relatively rarely, and the process is quite heterogeneous [12].

3.6 Schizophrenia and hallucinogen use

There is not sufficient evidence that Lysergic acid diethylamide (LSD) causes prolonged psychotic symptoms. The frequency of hallucinogen-induced psychosis changing to a diagnosis in the SZ spectrum during eight years has been reported as %24. The most common diagnosis is schizoaffective disorder, and mood symptoms are present [12].

3.7 Schizophrenia and opioid use

The Epidemiological Field Study found more associations between opioid use disorders and SZ than previous studies [5]. The CATIE study, on the other hand, found low levels of opioid abuse or dependence in participants with SZ [27]. In the 1970s, an investigation of methadone causing elevated prolactin levels demonstrated its dopamine-blocking effect. The inhibition of adenylate cyclase by antipsychotic drugs such as haloperidol, similar to methadone and other opioids, has led to the theory that opioid agonists have antipsychotic effects. The combined use of methadone and neuroleptics in the treatment of SZ was investigated in the 1980s. In a study conducted with a limited number of SZ patients, it was reported that methadone added to chlorpromazine had a moderate but statistically significant effect on psychotic symptoms [28]. In a study conducted in 1998, it was reported that individuals with a history of mental illness who stated that they did not use opioids in the baseline used more opioids after a 3-year follow-up than those who did not have a history of mental illness [29]. Although it is known that people with a psychiatric history use opioids more frequently, limited data is of the relation with psychotic disorders.

3.8 Schizophrenia and use of other substances

Abuse of anticholinergic drugs has been reported primarily in patients with a psychiatric diagnosis [30]. It is unclear whether patients use these drugs to treat their extrapyramidal symptoms or to treat their negative symptoms. It has been reported that the negative symptoms of schizophrenic patients with anticholinergic drug abuse are more dominant, and this supports the theory that cholinergic hyperactivity has a significant effect on the negative symptoms of SZ [31]. There is limited information about the use of other substances in patients with SZ. In a study by Warner et al., the rate of inhalant use in individuals with SZ was found to be 29.1% [32].

3.9 Treatment

Carrying out the appropriate treatment for both diseases by the same treatment team will also allow the continuation of outpatient treatment in the long term. According to neurobiological approaches, dysfunction in the brain reward circuit should be targeted to reduce substance use in patients with SZ. In addition to drug therapy, general and specific psychotherapeutic, socio-therapeutic and occupational therapy should also be applied. General principles of treatment for intoxication and withdrawal can also be applied to patients who are diagnosed with SZ.

However, if the patient continues to receive antipsychotic treatment, drug interactions should be taken into consideration. Benzodiazepines should be preferred, especially in alcohol withdrawal syndrome, because they show fewer interactions and prevent seizures that may develop due to withdrawal and delirium [33–35]. It is not necessary to use higher doses of antipsychotics in the treatment of psychotic symptoms compared to patients without substance use disorder comorbidity. Although high doses of antipsychotics successfully treat psychotic symptoms, they seem far from eliminating the psychokinetic effects of the substances. Recent reviews in schizophrenic patients with substance abuse indicate that second-generation antipsychotics (SGAs) are superior to first-generation antipsychotics (FGAs) because of their different receptor profiles. There is limited data showing that FGAs reduce substance abuse in patients with SZ, whereas there is data showing that haloperidol treatment increases the rate of smoking in patients with SZ [36]. Clozapine seems to be the most appropriate treatment for SZ patients with comorbid substance use disorders. It has been shown that clozapine decreases the craving for cocaine use [37], the rate of smoking [38], the rate of substance use [38–42], and increases the number of days without drugs [40, 41]. The level of evidence regarding the effectiveness of other atypical antipsychotics on substance use is still weak. Cases of quetiapine abuse have been reported, and it should be questioned if it is being used according to the prescription [42]. In the treatment of alcohol use disorder accompanying SZ, a limited number of studies in which naltrexone, disulfiram, and Acamprosate were added to antipsychotic treatment showed that these treatments were well tolerated and had a positive effect [33]. Using psychopharmacological agents in the smoking cessation treatment of patients with SZ may be more frequently required compared to the general population. Nicotine replacement therapies can be used alone or in combination with a therapy method, bupropion and varenicline, and can be used effectively and reliably in patients with dual diagnoses [43]. Substances used can affect the effectiveness of antipsychotic treatments. Smoking causes a decrease in blood levels of haloperidol, fluphenazine, olanzapine and clozapine [44]. Quitting smoking will cause an increase in drug blood levels. On the other hand, caffeine acts as a competitive inhibitor for CYP1A2, which acts in the metabolism of antipsychotics. Therefore, caffeine increases the blood levels of antipsychotics such as olanzapine and clozapine [45]. All substance use disorders, especially cocaine, accompanying SZ increase the possibility of extrapyramidal side effects due to antipsychotic drugs [46].

4. Psychopharmacology of schizophrenia

SZ is a chronic, often debilitating, and relapsing mental disorder, approximately with a lifetime prevalence near 1% [47]. Relatively specific core symptoms of SZ manifest as a combination of positive symptoms (hallucinations, delusions, impaired thinking, disorganized behavior) negative symptoms (affective blunting, emotional withdrawal, poverty of speech, anhedonia and apathy) and/or cognitive impairment (learning, memory, attention and executive functions deficits) [48]. Typical and atypical antipsychotic medications are gold standard in the management of the disease. An essential difference between typical and atypical antipsychotics is that, atypical antipsychotics with lower affinity [49] and faster dissociation rate [50] at the dopamine D2 receptor, may cause minimal extrapyramidal side effects (EPS) or prolactin elevation, decreased cognitive impairment and greater improvement

in negative symptoms although there are some exceptions [50]. Since treatment of negative symptoms and cognitive disorders keep on being a serious problem by current antipsychotic drugs, and positive symptoms are resistant to currently available medications in a substantial number of patients, it challenges the researches to investigate more effective and better-tolerated novel targets used as either monotherapies or as adjunctive treatments added to currently available antipsychotics [51]. The use of adjunctive pharmacological agents might offer a viable approach for cognitive functions since they can be used to modulate specific neurotransmitter systems hypothesized to be associated with cognitive functions. Unfortunately, at the present day there is no obvious or best choice of drug in antipsychotic medication.

4.1 Mechanism of action of antipsychotic drugs

SZ involves alterations of dopamine neurotransmission in brain circuits with excess dopaminergic activity in the mesolimbic pathway responsible for positive symptoms and reduced dopaminergic signaling in the mesocortical pathway causing negative symptoms, complemented by the glutamatergic hypothesis which considers changes in prefrontal neuronal connectivity involving glutamatergic neurotransmission at NMDA receptor [52]. Thus, the antagonism of D2 receptors in the mesolimbic pathway will produce reductions in dopamine activity and psychotic symptoms [53]. All known antipsychotic drugs (APDs) with documented efficacy on positive psychotic symptoms have affinity for the D2 receptor and fully or partially block the actions of dopamine [54]. D2 receptors mediate their physiological actions through both G-protein dependent and independent signaling [55]. Thus, drug development efforts now target novel important signaling mechanisms of G protein-coupled receptors (GPCRs) mainly dopaminergic, serotonergic, cholinergic, glutamatergic, adenosine and other neurotransmitter systems.

4.2 Dopaminergic mechanisms

All APDs increase the turnover and the release of dopamine as a consequence of postsynaptic dopamine receptor blockade in certain brain regions. The three principal dopaminergic pathways in the brain play role in the antipsychotic activity of antipsychotic drugs to different extends: The nigrostriatal pathway is considered to be responsible for extrapyramidal symptoms and cognitive function, in addition long-term blockade of this pathway may cause up-regulation resulting with tardive dyskinesia; The mesolimbic pathway is thought to be involved in delusion and hallucinations of psychosis, emotional activity, reward and motivation (blockade of D2 receptors in this pathway is thought to mediate the antipsychotic efficacy of the antipsychotic drug and its ability to reduce or block positive symptoms); The mesocortical pathway is thought to be involved in the production of positive and negative psychotic symptoms and cognitive processing (blockade of D2 receptors in this pathway may produce blunting of emotions and cognitive side effects, limiting the negative symptoms of SZ [56, 57]. It should be pointed out that antipsychotic effect necessitates the modulation of D2 receptors. All APDs are mixed D2/D3 and often also Dopamine 4 (D4) ligands with Dopamine (D3) and D4 subtypes having attractive limbic/cortical expression pattern. No evidence exists supporting the efficacy of a selective D3 antagonist by itself on psychotic symptoms, but it may enhance the efficacy of D2 antagonism and reduce EPS potential [48].

4.3 Serotonergic mechanisms

Serotonin 2A (5-HT2A) antagonism is the most investigated mechanism since it is the main driver of atypicality [58]. Atypical antipsychotics almost always have higher affinity for 5HT2A receptors than they do for D2 receptors. 5-HT2A receptor blockade along with weaker D2 receptor blockade may play role in the ability of atypical APDs to increase dopamine levels in the medial prefrontal cortex while exerting weaker effect on limbic dopamine efflux. This may contribute to their advantages for cognition, negative symptoms and antipsychotic activity. Partial agonist actions at 5HT1A receptors and partial agonist actions at D2 receptors in addition to 5HT2A antagonism, can also mediate the atypical antipsychotic clinical profile of low EPS and less hyperprolactinemia with comparable antipsychotic actions [51, 56, 57]. Blocking 5HT2C receptors stimulates dopamine and norepinephrine release in prefrontal cortex, and has pro-cognitive but particularly antidepressant actions. Some atypical APDs have potent 5-HT2C-antagonist activity, including those with known antidepressant action (e.g. quetiapine and olanzapine [59].

A few APDs have moderate affinity for (and partial agonist activity at) 5-HT1A receptors (e.g., clozapine, ziprasidone, quetiapine and aripiprazole). Atypical APDs with either potent 5HT2A antagonism or potent 5HT1A agonist/partial agonist properties, or with both actions, have a reduced incidence of EPS and thought to improve negative symptoms and cognitive impairment [51, 57, 59]. Serotonin 2C (5-HT2C) antagonism may contribute to weight gain induced by several atypical APDs [2] while Serotonin IA (5-HT1A) agonism may be responsible for reducing the potential for weight gain of atypical APDs [57].

4.4 Adrenergic receptors

All atypical antipsychotic has at least moderate binding potency to α1-adrenergic receptors which contributes to their side effects. α1 antagonist activity may have implications for lowering EPS. Several atypical antipsychotics also have α2 antagonist properties and attenuation of inhibition of noradrenergic and serotonergic neurons by α2 antagonists is believed to improve mood and may contribute to the beneficial effects of antipsychotics on mood [51, 56, 59].

4.5 Acetylcholine receptors

Blockade of muscarinic receptors by some APDs are useful in the treatment of SZ especially by limiting EPS. However, affinity for the muscarinic receptor results with increase in unacceptable autonomic side effects and differences in affinity for the muscarinic receptor subtypes significantly affects the properties of the drug. Muscarinic antagonists used for treating EPS have been reported to ameliorate negative symptoms of SZ [13] while muscarinic M1 receptor agonism might be beneficial in treating the cognitive dysfunction as well as the psychotic symptoms in SZ [60].

4.6 Drug development strategies

Since several different elements of the neural circuitry underlie the multiple deficits of SZ, treatment requires drugs acting through different mechanisms. Comprehensive research on GPCRs resulted in the exploration of novel important

signaling mechanisms of GPCRs which are crucial for drug discovery. It seems rational to develop molecules having a little affinity to D2 receptors and also binding to one or more preferred targets such as 5-HT1A, 5-HT2A, 5-HT2C, 5-HT6, 5-HT7, glutamatergic and/or nicotinergic receptors, while avoiding interaction of targets such as α1-adrenergic, H1, M1 and M3 receptor activity. To design single-target agents that can be used to augment multi-target agents is another option in APD development. Single-target vs. multi-target agents will likely remain at the main point of APD development. Since cognitive deficits in SZ are widely prevalent and appear to be correlated with social and occupational function, improving cognitive function should be a characteristic of all newly developed drugs used for the treatment of SZ [54, 61].

4.7 Dopaminergic targets

Since D2 receptor has been the 'Holy Grail' for the development of APDs, pharmacologic initiatives to reduce neurotransmission through the D2 receptor represent the only proven therapeutic mechanism for psychoses. D1 receptor antagonist or agonist, D2 receptor partial agonist, D3 receptor antagonist and D4 receptor antagonist molecules are new targets of drug development for APDs. The newest novel group of antipsychotic drugs, aripiprazole, brexpiprazole and cariprazine unlike others, are not dopamine. D2 receptor antagonists but D2 partial agonists [62]. The D3 receptors, with similar properties as D2 receptors, appear to be promising candidates for antipsychotic drug discovery. D5 receptors, with similar properties with D1 receptors have attracted attention for the treatment of cognitive disturbances, with an effect likely mediated through enhancement of NMDA receptor function [48, 57].

4.8 Serotonergic targets

5-HT3 receptors regulate inhibitory Gamma Aminobutyric Acid (GABA) interneurons in various brain areas that in turn regulate the release of a number of neurotransmitters. Blocking 5-HT3 receptors on GABA interneurons increases the release of serotonin, dopamine, norepinephrine, acetylcholine and histamine in the cortex and is thus a novel approach to a pro-cognitive agent [57]. 5-HT4 receptors, expressed in nigrostriatal and mesolimbic systems, can modulate the release of Ach, dopamine, GABA and serotonin. 5-HT4 receptors may be an attractive target for improving cognition in SZ, since currently available atypical ASDs generally lack significant affinity for 5-HT4 receptors [63]. 5-HT6 receptor antagonists have been proposed as novel adjunct targets for antipsychotics in enhancing cognitive function and/or treating negative symptoms in SZ [57, 64]. 5HT7 receptors, important regulators of serotonin release, exert significant roles in circadian rhythms, mood and sleep. Several APDs are 5HT7 antagonists and may have important roles in learning and memory [57].

4.9 Glutamatergic targets

Glutamatergic system, particularly by antagonizing NMDA sensitive glutamate receptors, is another neurotransmitter system underlying pathogenesis of SZ. Under activity of the mesocortical dopamine system may mediate the negative, cognitive and affective symptoms of SZ and could also be linked to hypo functioning of NMDA

receptors at different GABA interneurons. Thus, disturbances in glutamate signaling may be an attractive drug target for SZ due to its key role in the path mechanism of this disease especially in regards of cognitive impairment and negative symptoms [65, 66]. The glycine regulatory site agonists (e.g. glycine-cyclomerized-serine and D-alanine) are potential targets for APD development since they augment NMDA-receptor mediated activity. Metabotropic glutamate receptor (mGluR),another class of glutamate receptor, presynaptic antagonists/postsynaptic agonists may provide a new alternative monotherapy for the treatment of SZ [57, 67]. α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors are glutamate receptor subtypes, leading to NMDA receptor activation. Ampakines, a class of compounds that enhance receptor function, represent another potential target for treatment of SZ with expectance of more efficacy for cognitive symptoms and without exerting activation of positive symptoms or neurotoxicity [57, 68]. Since glycine transporter inhibitors (GlyT1 e.g. sarcosine, bitopertin) increase NMDA neurotransmission, it is expected that they will be able to adequately reduce the hypo functioning of NMDA receptors in order to lead improvement, especially in the negative and cognitive symptoms of SZ, perhaps also augment the improvement in positive symptoms achieved by treatment with atypical antipsychotics, and thus attract maximum overall efficacy in SZ [56, 69]. Glutathione precursor (N-acetylcysteine) could be also be of clinical benefit in the treatment of SZ by preventing oxidative stress and enhancing neurotransmission at NMDA-receptors [53, 70].

4.10 Other aminergic GPCR targets

Besides dopamine and serotonin receptors, other aminergic receptors i.e., adrenergic, cholinergic, muscarinic and histaminergic receptors are also linked to SZ. Potential benefits of α2-adrenergic receptor agonists or antagonists in SZ remains unclear. α7 nicotinic, acetylcholine (ach) receptor agonists (3-2,4-dimethoxybenzylidene anabaseine, tropisetron) and α4-β2 nicotinic receptor agonists (varenicline) are possible adjunctive targets to APDs for the treatment SZ [54]. Modulation of dopamine and glutamatergic neurons by cholinergic muscarinic receptors (e.g. muscarinic M1/M4 agonist xanomeline) has been new targets of APD development [60, 71]. Results of attempts aiming to increase ach receptors concentration and potential activity at both nicotinic and muscarinic receptors by Ach esterase inhibitors for improving cognitive function in SZ are controversial [51]. There is a correlation between increased histamine occupancy and decreased cognitive performance. Antipsychotics have moderate antagonistic potency for H1 receptors with some exceptions [59]. H3receptor antagonists/inverse agonists are targets of drug researches as a possibly novel class of drugs with precognitive properties [53, 72]. Molecules avoiding H1 receptor affinity and 5-HT2C antagonism might be useful in preventing antipsychotic-induced sedation and weight gain [73].

4.11 Other targets

Agents that increase GABAergic inhibition of cortical pyramidal cells have been hypothesized to improve working memory and other cognitive impairments in SZ. Phosphodiesterase (PDE) inhibitors, improve neurotransmission by affecting intracellular second messenger signaling and particularly PDE2, PDE4, PDE5 and PDE10 inhibitors seem promising for treating cognitive symptoms of SZ [27]. Neurokinin-3 (NK3) tachykinin receptor antagonist (osanetant, talnetant),

estrogen, oxytocin, secretin, erythropoietin, neuroactive steroids, omega-3 fatty acids and ginkgo are adjunctive candidate modulators of SZ. Complementary minocycline, anti-inflammatory agents (celecoxib) and COMT inhibitors (tolcapone, entacapone) might have benefit effects in SZ and it is postulated that immunotherapy is a treatment option for this syndrome [74]. Already there exists numerous updated guidelines for the pharmacological treatment of patients with SZ although consistent and contradictory recommendations exist between them [75]. The discovery of effective novel therapeutic agents for the treatment of SZ will require our understanding of the molecular and functional pathophysiological mechanisms playing role in SZ.

Since several different elements of the neural circuitry underlie the multiple deficits of SZ, radical new approaches require a deeper understanding of the path mechanism and causes of the disorder that are still insufficiently understood. Although D2 antagonist/partial agonist properties can explain the antipsychotic efficacy for positive symptoms as well as many side effects of antipsychotics, and the 5HT2A antagonist, 5HT1A partial agonist and muscarinic antagonist properties can explain the reduced propensity for EPS or elevating prolactin by various antipsychotics, many additional pharmacologic properties of these drugs also play role. Glutamatergic system, particularly by antagonizing NMDA sensitive glutamate receptors, is an attractive neurotransmitter system affecting psychosis in SZ. Cholinergic, muscarinic, GABA and glutamate receptors also play role in the psychotherapy of SZ. They are capable to modulate antipsychotic drug action, including EPS and cognition, through several direct and indirect mechanisms. Current efforts in drug design against SZ focus on cognitive behavioral psychotherapy in order to strengthen the patient's capacity for normal thinking using mental exercises and self-observation besides searching for compounds treating negative symptoms and as well as better tolerated. We are aimed to overview of different strategies and targets under investigation for the development of novel psychological therapies in the treatment of SZ involving mainly novel mechanisms of GPCRs signaling.

5. Genetics and epigenetics in schizophrenia

SZ is a severe mental-psychiatric disorder for which there is no definite knowledge about its underlying mechanisms. Although the complex interactions of genetic and environmental factors play a role in the etiology of SZ, studies on twins have shown that hereditary factors are very important in terms of susceptibility to SZ. Accumulating data from genome-wide association studies (GWAS) are constantly decoding SZ risk genes. Especially with the widespread use of new generation sequencing systems, it has been shown that more than 200 loci may play a role in the etiology. In addition, epigenetic factors should not be forgotten. Biomarker studies (Brain Derived Neurotrophic Factor (BDNF), MB-COMT, COMT, Reelin (RELN) and The serotonin receptor subtype 2 (HTR2) etc.) have proven that DNA methylation and histone acetylation are also effective in the development of SZ. The use of epigenetic treatments in practice and the development of gene therapy options provide hope for the treatment of such neuropsychiatric diseases. SZ is a severe mental-psychiatric disorder for which there is no definite knowledge about its underlying mechanisms. Although the complex interactions of genetic and environmental factors play a role in the etiology of SZ, studies on twins have shown that hereditary factors are very important in terms of susceptibility to SZ. Heritability is the proportion of variance,

in a multifactorial threshold model, explained by genetic variability. The concordance rates of SZ for monozygotic twins have been found to be approximately %50–60, compared with %6–%10 in dizygotic twins. Additionally, studies have shown elevated rates of SZ and SZ spectrum disorders in biological families of schizophrenic adoptees compared with biological families of control adoptees, coupled with low, equivalent such rates in adoptive families of both types of adoptees (**Table 3**).

The consanguineous relationship seems to be valid not only for the disease but also for the inheritance of some brain morphology changes that may be related to the disease. In a neuroimaging study of families with multiple affected individuals, the brain structures of patients and unaffected relatives showed similar aberrations to their relatives with SZ, and the greater the degree of kinship, that is, the greater the genetic similarity, the more similar the degree of deviation was [76–78]. Considering all the information accumulated so far, it is known that SZ is familial and genes make the most important contribution to the risk of the disease. There are different chromosomal regions pointed out by linkage studies. Accumulating data from GWAS are constantly decoding SZ risk genes. Especially with the widespread use of new generation sequencing systems, it has been shown that more than 200 loci may play a role in the etiology. Copy Number Variations (CNVs) are stretches of genomic deletions and duplications ranging from 1 kb to several Mb, and thus are likely to have larger phenotypic effects than Single Nucletoide Polymorphisms (SNPs). A well-known CNV is the 22q11 deletion, 20–30% of people with it having SZ [79]. Additionally, There are many CNV Loci associated with SZ (**Table 4**) [80–82].

This study identified 108 independent genomic risk loci, localizing the search to genes that are current or promising targets for treatment (DRD2, GRM3, NOTCH4), genes more widely involved in glutamatergic neurotransmission (GRIN2A, SRR, CLCN3, and GRIA1), and unexpected candidate mechanisms involving neuronal calcium signaling (CACNA1C, CACNA1l, CACNB2, RIMS1) and broader synaptic function (KCTD13, CNTN4, PAK6). When considering all researches, studies have indicated that APOE, BDNF, CHRNA7, COMT, DISC1, DRD2, HTR2A, and NRG1 genes are as strong candidate genes in the etiology of SZ [83–85]. Considering all studies, it can be said that SZ is a multigenic, multifactorial neuropsychiatric disease.

Relation	**Risk (%)**
General population	0.86
Identical twins	57.70
First-degree relatives	
Brothers and Sisters	8.5
Children	8.2
Third-degree relatives (first cousin)	2.9
Risk of offspring of 0–2 schizophrenic parents	
Neither parents schizophrenic	8.2
One parent schizophrenic	13.8
Both parents schizophrenic	36.6

Table 3.
Risks to relatives of those with schizophrenia by Dr. Özdemir.

CNV Loci	Related gene(s)/syndromes
1q21.1 deletion/duplication	Connexin50, GJA8
2p16.3 deletion	NRXN1
3q29 deletion	PAK2, DLG1, FBXO45
7q36.3 duplication	VIPR2
15q13.2 deletion/duplication	Williams–Beuren Syndrome
16p13.11/16p11.2 duplication	—
17q12 deletion/duplication	Many genes
22q11.2 deletion	Di Geoge syndrome

Abbreviations: Connexin50, Gap Junction Protein Alpha 8 (GJA8), Neurexin 1 (NRXN1), The p21-activated kinase 2 (PAK2), Discs large homolog 1 (DLG1), F-Box Protein 45 (FBXO45), Vasoactive intestinal peptide receptor 2 (VIPR2), Copy Number Variations (CNVs). The Psychiatric Genomics Consortium (PGC) published the most extensive GWAS report on SZ in 2014 (up to 36,989 cases and 113,075 controls).

Table 4.
The most important CNV loci associated with schizophrenia by Özdemir.

Gene	DNA metilation status	Brain region
RELN	Hyper-methylation of promoter in SZ	Frontal/occipital lobe pre-frontal cortex
MB-COMT	Hypomethylation of MB-COMT promoter	DLPFC (Broadman's area46)
SOX10	Hyper-methylation of SOX10 in SZ	Prefrontal cortex (BA10)
FOXP2	Hyper-methylation of FOXP2 in SZ	Parahippocampus gyrus

Abbreviations: reelin (RELN), SRY-box transcription factor 10 (SOX10), Forkhead box protein P2 (FOXP2), schizophrenia (SZ).

Table 5.
Candidate genes in DNA methylation studies by Özdemir.

In addition, epigenetic factors should not be forgotten Changes in DNA methylation and other epigenetic factors (histone acetylation, miRNA, etc.) are thought to be more common and more effective than expected in the etiology of SZ. The advancement of next-generation sequencing technology has provided an opportunity for genome-wide methylation studies, termed epigenome-wide association studies (EWAS). DNA methylation changes in SZ have been explored using candidate genes strategy and whole genome approaches and some candidate genes given in **Table 5**.

Biomarker studies (BDNF, MB-COMT, COMT, RELN and HTR2 etc) have proven that DNA methylation and histone acetylation are also effective in the development of SZ. The use of epigenetic treatments in practice and the development of gene therapy options provide hope for the treatment of such neuropsychiatric diseases.

microRNAs (miRs) are small single-stranded non-coding RNA molecules that functions in RNA silencing and post-transcriptional regulation of gene expression. They are approximately 22 nucleotides of length and transcribed from different regions of the genome and believed to have a crucial role in the development of central nervous system reported that the upregulation of miR-132 in the mouse led to the downregulation of its target genes during brain development. it is found substantial correlation networks between miR-92a, miR-495, and miR-134, and their target genes [B-cell lymphoma/leukemia 11A (BCL11A), Proteolipid Protein 1

Upregulated miRNAs	Downregulated miRNAs
miR-21-5p, miR-22-3p, miR-30d-5p, miR-30e-5p, miR-34a, miR-92a-3p, miR-106b, miR-122, miR-130a, miR-130b, miR-137, miR-181b-5p, miR-195-5p, miR-193-a-3p, miR-193b, miR-502-3p, miR-652, miR-886-5p	miR-7, miR-9-3p, miR-20b, miR-24, miR-26b, miR-29a, miR-29b, miR-29c, miR-30a-5p, miR-30b, miR-30d, miR-30e, miR-92, miR-128, miR-132, miR-132-5p, miR-134, miR-181b, miR-195, miR-200c, miR-212, miR-664-5p, miR-1271, miR-432,

Abbrevations: microRNA (miR).

Table 6.
miRNA dysregulation in schizophrenia by Özdemir.

(PLP1), and Synaptotagmin 11 (SYT11)] in pathways involved in oligodendrocyte function and neurodevelopment. Apart from these miRNAs, many miRNAs were found to be associated with SZ and could be biomarkers in the diagnosis of SZ (see in **Table 6**) [86–90].

Technological advances in medical genetics (NGS, whole exome and genome sequence analysis) facilitate the identification of candidate genes and the determination of etiology in SZ and other neuropsychiatric diseases. Especially with studies in the fields of epigenetics (DNA methylation, histone modification, miRNA) and gene therapy, genetics will be effective not only in the diagnosis of these diseases but also in the treatment management.

6. In-silico applications in schizophrenia and future perspectives

Because of the variability of this mental condition and the lack of particular useful biomarkers, diagnosing SZ is a difficult task. A few clinical signs, including physical, psychiatric, and psychological markers, must be investigated to diagnose SZ [91–93]. Various diagnostics, such as blood testing and medical imaging, are included in clinical evaluations [93, 94]. If the doctors cannot uncover a physical cause for the patient's suspected SZ symptoms, they may refer them to a psychiatrist, psychologist, or another expert in the field. Clinical interviews based on the diagnostic and statistical manual (DSM-IV) of mental disorders undertaken by clinical psychiatrists to diagnose patients with SZ are the mainstay of psychological assessment [95, 96]. Another major group of procedures capable of diagnosing SZ is functional and structural neuroimaging techniques [97, 98]. Structural neuroimaging modalities primarily comprise structural magnetic resonance imaging (sMRI) [99–101] and diffusion tensor imaging (DTI) [102, 103], which, due to their high spatial resolution, display the anatomy of the human brain and its structural connectivity respectively. Overall, structural neuroimaging modalities based on MRI are useful for visualizing white matter (WM), gray matter (GM), and CSF tissues of the brain, as well as investigating their anomalies [104, 105].

Functional neuroimaging modalities for the diagnosis of SZ include electroencephalography (EEG) [106], magnetoencephalography (MEG) [107], functional near-infrared spectroscopy (fNIRS) [108, 109], and functional MRI (fMRI) [110, 111]. The use of MEG and fNIRS to diagnose SZ has been limited due to their high cost and lack of accuracy. Nowadays, computer-aided diagnosis systems (CADS) have been proposed to assist clinicians in diagnosing SZ automatically utilizing modern image processing and AI approaches [112–114]. To produce extremely

accurate and robust CADS, researchers used traditional machine learning (ML) and deep learning (DL) techniques [115]. Machine learning (ML) and artificial intelligence have recently been used for the diagnosis, monitoring, and prognosis of a variety of disorders, including SZ since these approaches, perform well in detecting a link between disease symptoms and disease. The results of studies using magnetic resonance imaging data and physiological signals as input data are given. To anticipate and monitor SZ, ML is used to extract key characteristics. A wide number of research suggest that a support vector machine, deep neural network, and random forest can accurately predict SZ with a 70–90% accuracy. Finally, the findings suggest that machine learning technologies offer clinicians credible responses when making judgments concerning SZ patients. In the field of biological psychiatry, there is a rising interest in using AI and machine learning [116–119]. Researchers in machine learning and artificial intelligence (ML and AI) use mathematical models to extract attributes or features from signals and pictures to establish links between the characteristics and brain state to evaluate if the brain is normal [120]. Scientists are interested in ML because certain ML algorithms can identify nonlinear correlations among characteristics, making it a great tool for unraveling patterns in SZ datasets. These, in turn, can anticipate disorders like SZ and track the nonlinear character of a condition. Support vector machine (SVM), random forest (RF), Naive Bayes (NB), artificial neural network (ANN), logistic regression (LR), and deep neural network (DNN) approaches are examples of extremely accurate machine learning methods. A CNN architecture is demonstrated in **Figure 2**.

Machine learning (ML) may be used to create computer-assisted diagnostic tools for clinical usage and to investigate disease pathophysiology. By allowing researchers to tackle the tremendous complexity of EEG data, machine learning has changed the area of SZ. Traditional machine learning (non-deep learning (DL) algorithm) has been the method of choice in EEG analysis for the past few years. It's been mixed and matched using a variety of feature extraction techniques [121–122]. DL algorithms have been widely used in medical image and signal processing in recent advancements, indicating that they offer a lot of research potential. In the vast majority of circumstances, they outperform standard machine learning algorithms. Many researchers have utilized DL in the field of EEG to investigate mental health to diagnose and classify diseases [123–126].

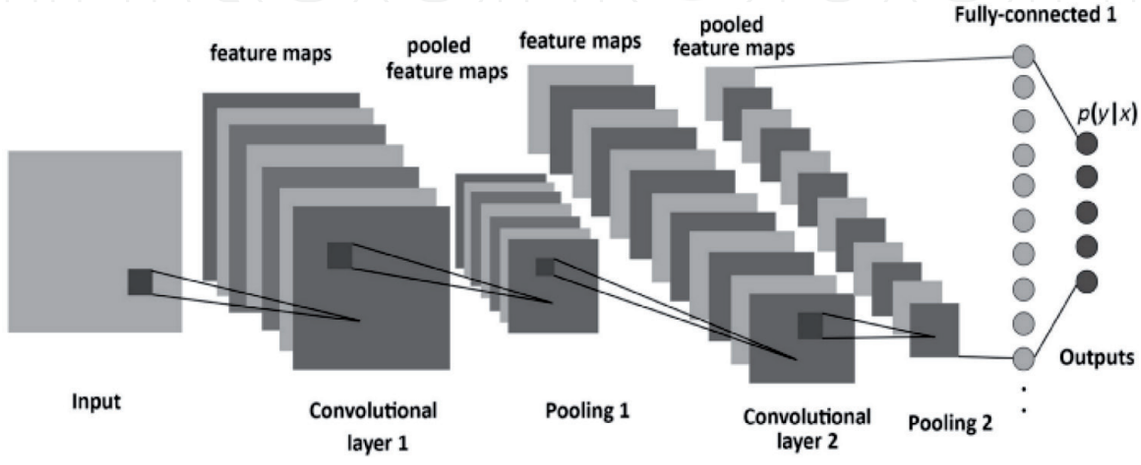

Figure 2.
A structure of a convolutional neural network by Dr. Ergüzel.

6.1 Entropy

EEG signals are studied utilizing changes in signal time series in time-domain feature extraction methods. The irregularity or unpredictability of brain activity is reflected in the EEG's complexity. Many researchers use nonlinear analytic methods to analyze EEG data as nonlinear theory continues to progress and evolve. Entropy is a nonlinear analytic technique for determining complexity. Entropy is the most widely used feature index among time-domain characteristics, and it is widely used in an illness diagnosis. Fuzzy entropy (FuzzyEn) is a regularly used entropy that was built based on other entropies. They have good resilience and high antinoise ability, and the algorithm complexity is lower than other entropies such as information entropy, sample entropy, and FuzzyEn. The entropy value measured by fuzzy entropy is continuously stable and less sensitive to the noise of EEG data, which makes it more suitable for analyzing chaotic signals. Previous studies have proven that the ability of FuzzyEn to detect and recognize signals is superior to the ability of other entropies for both epilepsy [36] and SZ [127]. The EEG signals of subjects with SZ were more random and, therefore, had a greater approximate entropy compared to the EEG signals of healthy subjects [128]. In addition, as previously reported using multiscale entropy, the complexity of schizophrenic patients is higher than that of the control group [129]. A broad overview Deep learning is the use of deep (multi-layer) artificial neural networks (DNNs), a class of problem-solving or system-modeling algorithms inspired by the nervous system that, unlike typical software, learn to solve issues through training [130]. DNNs have performed well in jobs that were previously regarded to be the only province of human competence. They have demonstrated exceptional performance in a variety of areas, including speech recognition [131], language translation [132], text understanding and generation [133], and object detection and recognition in images and videos [134].

DNNs are classed as feedforward or recurrent based on the direction of information flow. The information flow in feedforward DNNs is from input to output without any feedback loops (e.g., analogous to feedforward connections from V1 to V2 in the visual system). Feedforward multilayered DNNs are universal approximators, meaning that they can estimate with arbitrary precision any mapping (function) between inputs (e.g., pictures) and outputs (e.g., categories in a classification job) of a static system [135]. This type of DNN is most commonly utilized in activities that do not require any changes in time (e.g., image recognition). Recurrent DNNs, on the other hand, incorporate feedback loops in which layers communicate feedback information to each other and layers higher in the hierarchy.

Recurrent DNNs are universal approximators of dynamical systems, similar to feedforward DNNs [136]. This form of DNN is commonly employed in data that changes over time or is ordinal (e.g., weather forecasting or language translation). DNNs' ability to approximate complicated, multivariate, nonlinear systems vastly outperforms the results produced with classic shallow networks and machine learning methodologies, according to empirical studies. DNNs are end-to-end techniques, which means they not only learn to solve a job (e.g., speech recognition), but also automatically extract an optimal collection of features from the raw data that will be utilized to perform the problem. This is one of the reasons for their huge success in solving complex tasks.

DNNs can overcome various restrictions and biases influencing human-produced features by learning to extract features directly from raw data, resulting in improved performance with less task-specific customization. A DNN architecture that classifies

animal species using raw photos as input, for example, can be taught to handle a wide range of different tasks, such as face recognition, cell type classification, or MRI-based disease detection, with no changes to the output/classification layer. Because DNNs must learn a large number of parameters to differentiate important from irrelevant information in the often high-dimensional and noisy input space, the benefits of autonomous extraction come at the cost of enormous training datasets. Despite recent breakthroughs in autonomous DNN design [137, 138], three critical components of DNN design continue to rely heavily on human judgment: 2) learning rules (training algorithm): techniques for changing network weights during training; 3) objective functions: performance or cost measurements linked with an output (e.g., error, reward) that DNNs learn to minimize or maximize during training [139]. Deep learning can be used to delineate the structural characteristics of schizophrenia and to provide supplementary diagnostic information in clinical settings.

In **Figure 3**, the number of papers evaluated by the ANN architecture. (b) The ANN architecture's stated accuracy in the binary diagnostic test. (c) Several peer-reviewed studies are organized by data modality. (d) The binary diagnostic task's stated accuracy per data modality. (e) ANN architecture and publication year for several peer-reviewed studies. (f) A comparison of the accuracy reported by research employing datasets from various data collection sites when models were assessed on data from training sites (pooled sites evaluation) versus data from held-out sites that were not utilized during training (held-out sites evaluation) (leave-one-site-out evaluation). The sample sizes (number of participants) of the studies are represented by the size of the circles in panels (b) and (d), and the orange circles emphasize the five studies indicated in panels (a) (f).

6.2 Metaverse

SZ is a severe mental disorder characterized by positive (hallucinations, delusions, muddled thinking, and disorganized speech) and negative (affective flatness, alogia, and avolition) symptoms, as well as language impairment [141]. Individuals with SZ have a higher risk of suicide; the lifetime rate of suicide in those with SZ is around 10% [142]. The most obvious possible consequence of virtual contact is on psychoses, particularly those involving delusions and/or hallucinations. These are not the only conceivable outcomes, nor are they the most prevalent, so we must be explicit about this. Overuse of digital technology is linked to a variety of mental health disorders, including somatic symptoms (6%), sadness (4%), psychoticism (0.5%), paranoid ideation (0.5%), and serious mental disease (2%). However, psychoses are among the most significant, and they demand considerable thought, especially if a firm with an estimated 1.9 billion daily users suggests a shift to a digitally immersive experience. Facebook's Reality Labs Division appears to be sketching out the design of their metaverse and how it would simulate interacting with people, much as in a game.

In connection with excessive use of digital technology, schizotypal personality characteristics such as odd experiences, impulsive nonconformity, and cognitive disorganization have garnered attention [143]. Schizotypy is thought to be a subclinical illness related to SZ. Due to the complications that studies with SZ might cause, evaluating schizotypy is frequently done instead of examining patients with SZ. In one research, 6100 20- to 30-year-olds were assessed for problematic internet usage (PIU), depression, anxiety, and schizotypal features. PIU was present in around 30% of these patients. In addition to the well-known connections between PIU, sadness, and anxiety, 2, PIU was linked to schizotypal personality features. Another study looked at the relationship between schizotypy symptoms, Facebook use, and PIU7. Two hundred

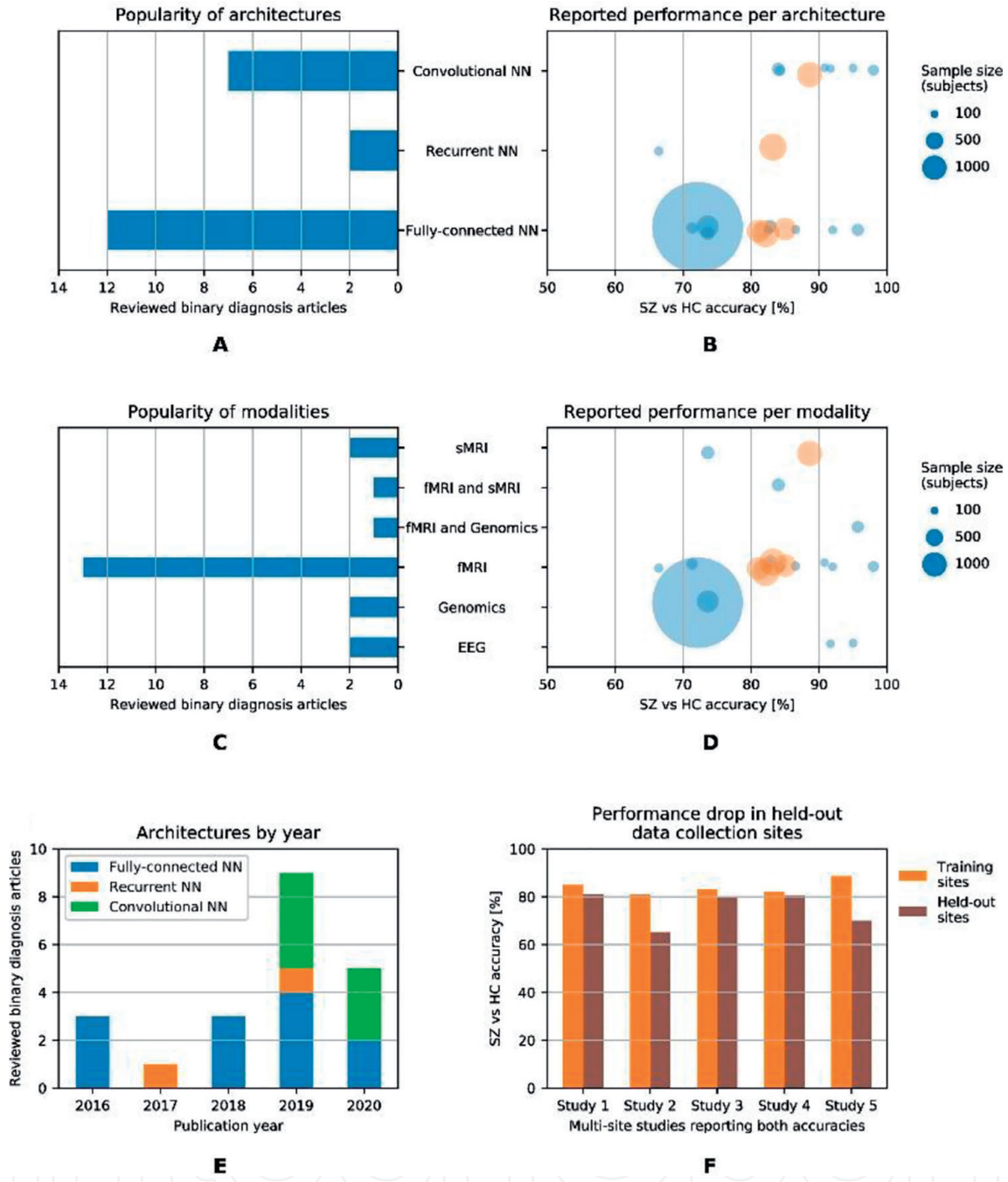

Figure 3.
Review of binary diagnosis of schizophrenic (SZ) patients against healthy controls (HC). (A) Number of reviewed articles by ANN architecture. (B) Reported accuracy of the binary diagnosis task by ANN architecture. (C) Number of reviewed articles by data modality. (D) Reported accuracy of the binary diagnosis task by data modality. (E) Number of reviewed articles by ANN architecture and publication year. (F) Comparison of the accuracy reported by studies using datasets from multiple data collection sites, when models were evaluated on data from collection sites used during training (pooled site evaluation) or on data from held-out sites that were not used during training (leave-one-site-out evaluation). In panels (B) and (D), the size of the circles represents the sample sizes (the number of subjects) of the studies, and the orange circles highlight the five studies showed on panel (F) [140].

seventy 18- to 30-year-olds took part in the study, and it was discovered that schizotypy levels predicted PIU as well as the frequency of Facebook use. PIU was better predicted by disorganized schizotypy. There is other research in this line, but the results are fairly consistent: There is a link between digital usage and schizotypy symptoms similar to SZ and other psychoses. Studies concentrating on subclinical symptoms related to

schizotypy are thought to have minimal significance for clinically relevant diseases. Concerning digital usage, there are various professionally validated descriptions of SZ and psychoses. One clinical case series published in a recognized publication described two individuals who suffered Facebook-related delusions. " the backdrop of the nature of social networking media and the internet, including instances of how they have been utilized therapeutically, as well as the potential for negative usage," the authors said. While severe mental symptoms such as these are infrequent in PIU patients, around 0.5 percent report delusions and psychoses2. Even if 10% of the almost two billion daily Facebook users acquire PIU, it equates to around 1 million persons with psychosis or comparable symptoms who engage in virtual worlds regularly.

What can we draw from this research in the context of immersing a large number of social media users in a metaverse? At most, such an atmosphere may provide a temporary haven' for persons suffering from schizophrenic-like symptoms. It remains to be seen whether this makes the metaverse a safe place for other individuals. At worst, absorption in this digital environment may raise the probability of becoming disconnected from reality, resulting in delusional or psychotic symptoms. Once again, we are witnessing a situation in which a digital technology corporation proposes a product with a high potential for harm to public health that has not been subjected to adequate scientific risk assessment. It's unclear whether Facebook's investment in 10,000 employment in nations that have agreed to develop this technology has anything to do with it. The metaverse might become a psychotic sanctuary, feeding a certain form of sadism. It has the potential to send our society into a state of SZ, separating us from reality and transforming truth into a succession of delirious interpretations, ending in paranoia, delusions, and yet-unknown diseases in both realms. According to a new paper published in the journal The Lancet Psychiatry, researchers conducted the largest clinical trial employing VR therapy to treat individuals suffering from psychosis and SZ. The experiment was part of the game change program, created by the University of Oxford and the Oxford Health NHS Foundation Trust to treat agoraphobia, a typical symptom of psychosis [144].

7. Multimodal neuroimaging in schizophrenia

Multiple methods, and technologies that provide structural and functional data on neural mechanisms, including neuroimaging in general, electroencephalography (EEG), magnetoencephalography (MEG), functional magnetic resonance imaging (fMRI), positron emission (PET), diffusion tensor imaging (DTI) and noninvasive modalities. Although each modality provides different and valuable information about brain structures and/or activities, researchers have begun to combine multiple techniques called multimodal neuroimaging (MN) to understand brain dynamics in more detail and to overcome the limitations of modalities. Multimodal neuroimaging has several advantages over unimodal neuroimaging in providing more comprehensive information on quantifying, generalizing, and normalizing neural processes and structures, higher spatial and temporal resolution, and it has been shown to reduce the limitations of unimodal techniques. Multimodal neuroimaging; is thought to have the potential to shed light on the neuronal mechanisms underlying risky conditions such as structural and functional pathophysiological features, prefronto-temporal gray matter reduction, and impaired high-grade cognitive processing, and impaired dopaminergic-glutamatergic neurotransmission in schizophrenia patients [145]. Recent advances in machine learning techniques have allowed promising results for personalized prediction and characterization in patients with schizophrenia [146]. In

studies combining DTI and rest or task fMRI; DTI and task fMRI analyses revealed fractional anisotropy (FA) reductions in the right medial temporal lobe adjacent to the right parahippocampal gyrus, and fMRI was reported to reveal partial hypoactivation of prefrontal, superior parietal, and occipital in patients with schizophrenia [147]. DTI and fMRI at rest showed altered functional and anatomical connectivity in the medial frontal and anterior cingulate gyrus in patients with schizophrenia [148]. In the DTI and on-the-job fMRI study, it was reported that significantly reduced activation of the fronto-striato-cingulate network in patients with schizophrenia was associated with difficulties in making decisions under uncertainty. The same study shows that activation in parts of the fronto-striato-cingulate network is negatively correlated with an increased radial spread in temporal white matter [149]. Another similar study showed that the total connectivity of the thalamus to the lateral frontal cortex (LPFC) is reduced in patients with schizophrenia. Total thalamocortical connectivity to the LPFC predicts working memory performance and also correlated with LPFC BOLD activation. The correlation with BOLD activation of the LPFC is emphasized in patients with schizophrenia [150]. A proposed new framework for the classification of schizophrenic patients and healthy control subjects based on using both fMRI and band-limited envelope correlation measures in MEG to interrogate functional network components at rest provides evidence that the combination of these two methods is useful for estimating patients with schizophrenia. The results suggest that the combination of these two methods provides valuable information that captures key features of brain network connectivity in schizophrenia. Independent component analysis (ICA)-based functional network connectivity (FNC) is a data-driven approach that summarizes the overall link between individual brain maps over time. Therefore, the FNC feature provides a picture of the connectivity pattern over time between individual components. The blood oxygenation level-dependent (BOLD) response as measured by fMRI, while allowing high spatial resolution maps, is limited because it is an indirect and slow physiological signal. Neural oscillatory activity, including rhythmic electrical activity in cell ensembles, is thought to underlie BOLD responses. This neural oscillatory activity occurs in the ~1–900 Hz band; such fast electrical signals can only be measured directly with techniques such as MEG, rather than fMRI. Measuring resting-state brain activity in a common subject sample using both fMRI and MEG combines the strengths of each modality, allowing the comparison of hemodynamic and electrophysiological effects. In this way, it provides important information about FNC, which is of particular importance for the study of schizophrenia and similar conditions. Recent studies show that connection dynamics can capture repetitive patterns of interaction between internal networks during undetectable rest or task-related experiments with FNC. These repetitive interaction patterns contain valuable information for the individual prediction of patients with schizophrenia [151]. Numerous studies combining fMRI data and MEG data consistently show auditory-sensory processing deficits in patients with schizophrenia. Poor sensory gating has been characterized not only as a deficit in selective attention and/or the formation of memory traces, but also as a useful biomarker of cognitive and social dysfunction observed in patients with schizophrenia. Electroencephalographic (EEG) and MEG studies of sensory gating implicate the temporal lobes, including the superior temporal gyrus, as the most likely neuronal producer of the sensory gating deficit. Hippocampal hypoactivation, which can be demonstrated by invasive methods in weak sensory gating, could be demonstrated by combining EEG, MEG and fMRI findings. Impaired sensory gating is thought to be an endophenotypic marker for schizophrenia. When the neural mechanisms underlying the multi-sensory

integration of auditory and visual stimuli in schizophrenia patients and healthy controls were examined using MEG and fMRI together with structural MRI (sMRI), it was shown that patients with schizophrenia had slower reaction times to multisensory stimuli than healthy controls. Because associated areas of the temporal lobe are essential for the integration of auditory and visual information, altered multisensory processing is consistent with the findings that patients with schizophrenia show functional and anatomical differences in the temporal lobes. The long-term goal is to identify local cortical deficiencies as well as deficiencies in cortical networks that lead to the abnormalities observed in patients with schizophrenia. Knowledge about these deficiencies, assessment of associations with neurochemical abnormalities, and ultimately, may lead to more individually targeted pharmacological interventions. The prefrontal cortex (PFC) and hippocampal structures play a central role in working memory and relational memory disorders exhibited in patients with schizophrenia. PFC and hippocampal functional deficiencies have traditionally been attributed to the characteristics of cortical structures. However, according to an alternative view, it has been reported that there is a functional disconnection between the frontal and temporal cortices (). In a study to demonstrate this, 3 T MRI was used [8]. Functional (ie, fMRI, PET) and biochemical/structural (ie, 1H-MRS, DTI, voxel-based morphometry (VBM). It is not possible to determine whether the disease underlies core deficits or represents compensation for overcoming primary functional deficits. However, MEG results suggest hypersynchronous prefrontal and temporal networks are thought to be consistent with the disconnected model of schizophrenia [98].

8. Conclusion

Over the last two decades, several trends have collided to raise questions about how the notions of schizophrenia, the schizophrenia spectrum, and the psychotic disorders spectrum should be viewed. These tendencies can be found in fields including genetics, neuroimaging, and data-driven computational investigations of numerous response systems. Growing evidence reveals that schizophrenia is a broad and heterogeneous condition that is part of a multi-faceted psychosis spectrum, rather than a single disease entity. The reliance on sets of symptoms and signs for defining a diagnosis, as well as the use of traditional diagnostic categories in analyzing clinical research grants, has slowed progress in explaining these varied developments. In order to address these issues this chapters covered the topic from different perspectives. The chapter takes a neurological approach to schizophrenia and discusses individualized treatment options from diverse perspectives. Genotyping and phenotyping keys are used to provide personalized treatment in the diagnosis and treatment of schizophrenia. The psychopharmacology of schizophrenia and the mechanism of action of antipsychotic medicines are discussed after comorbid schizophrenia in addiction with the use of numerous substances. In the last section, in-silico application and computational methodologies encompassing feature extraction process and destructive impact of metaverse are shared. Recent studies underline the success and contribution to biomarker extraction process of collaborative studies.

Conflict of interest

The authors declare no conflict of interest.

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