

# Advances in Schizophrenia Research

## Chapter 2

### Sum and Substance for Schizophrenia

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#### Abstract

Schizophrenia (SCZ) is a highly heritable, chronic, severe, disabling neurodevelopmental brain disorder with a heterogeneous genetic and neurobiological background, which is still poorly understood. Because schizophrenia has no distinguishing pathology or diagnostic criteria, it is difficult to relate gene changes to discrete physiological or biochemical changes associated with the disease. SCZ fits the profile of a complex disorder in which multiple genes interact along with environmental influences to produce a range of phenotypes. There is accumulating evidence that both common genetic variants with small effects and rare genetic lesions with large effects determine risk of SCZ. Thousands of common single nucleotide polymorphisms cumulatively could explain high percentage of the underlying genetic risk of SCZ. Therefore, it requires lifelong treatment, even when symptoms have subsided. Treatment with medications and psychosocial therapy help in managing the condition. In this review, we summarize the current understanding of genetic and pathogenesis of SCZ and highlight their potential role as diagnostic agents and therapeutic targets.

**Abbreviations:** SCZ: Schizophrenia; ID: Intellectual disability; DD: Developmental delay; BD: Bipolar disease; AD: Autosomal Dominant; SzGene: Schizophrenic genes; MTHFR: methylenetetrahydrofolate reductase gene; SNP: Single Nucleotide Polymorphism; in/del: insertion/deletion; DSM: Diagnostic and Statis-

tical Manual of Mental Disorders; APOL: Apolipoprotein; ncRNA: nonprotein coding RNA; hiPSC: human induced pluripotent stem cells

## 1. Introduction

Neurodevelopmental disorders are characterized by impairment of growth and development of the brain generally associated with cognitive, neurological, and psychiatric dysfunction. It can traverse, to varying degrees, diverse disease classifications including intellectual disability (ID), developmental delay (DD), autism, schizophrenia (SCZ), bipolar disease (BD), etc. Despite seemingly distinct primary diagnoses, considerable clinical heterogeneity, as well as overlap, has been appreciated for many years.

Schizophrenia is a chronic and severe mental disorder which affects thinking, feeling and action of an individual. Somebody with schizophrenia have difficulty in distinguishing between real and imaginary thinking and facing difficulty in expressing normal emotions in social circumstances. Many people with schizophrenia are not violent and do not present a danger expression to others. It is not caused by childhood experiences and lack of willpower. Although schizophrenia is not as common as other mental disorders, the symptoms can be very disabling.

### 1.1. Signs and symptoms

The signs of schizophrenia vary from patient to patients. Symptoms of schizophrenia usually start between ages 16 and 30. In rare cases, children have schizophrenia too. Either it develops slowly over months or years, or may appear very shortly. The disease may come and go in cycles of relapse and remission. The symptoms of schizophrenia categorized into three groups (i) positive, (ii) negative, and (iii) cognitive.

(i) Positive symptoms: “Positive” healthy people do not show symptoms of psychotic behaviors. People with positive symptoms may “lose touch” with some aspects of reality. It includes hallucinations, delusions, thought and movement disorders. (ii) Negative symptoms: “Negative” symptoms are associated with disruptions to normal emotions and behaviors. Symptoms include- “flat affect” (reduced expression of emotions via facial expression or voice tone), reduced feelings of pleasure, difficulty beginning and sustaining activities and reduced speaking. (iii) Cognitive symptoms: the cognitive symptoms of schizophrenia are delicate in some patients. Others, they are more severe and patients may notice changes in their memory or other aspects of thinking. Symptoms include- poor “executive functioning, trouble focusing, problems with “working memory” (Diagnostic and Statistical Manual of Mental Disorders-V (DSM-V).

It is well known that individuals with schizophrenia also demonstrate co-morbidity with

cognitive impairments of varying severities [1] as well as, in some cases, structural defects of the brain [2]. Behaviors that are early warning signs of schizophrenia include- hearing or seeing something that isn't there, a constant feeling of being watched, peculiar or nonsensical way of speaking or writing, strange body positioning, feeling indifferent to very important situations, deterioration of academic or work performance, a change in personal hygiene, appearance and personality, increasing withdrawal from social situations, irrational, angry or fearful response to loved ones, inability to sleep or concentrate, inappropriate or bizarre behavior, extreme preoccupation with religion or the occult.

## 1.2. Clinical features

Kraepelin, termed dementia as a cognitive disorder but Bleuler, emphasized that dementia which is replaced by schizophrenia is not a disease but it appears as a group of disease. Schizophrenia is a heritable disease, which often develops in young adults and is characterized by a group of symptoms including psychotic symptoms (hallucinations and delusions) and other symptoms such as severely inappropriate emotional responses, disordered thinking and concentration, erratic behavior, as well as social and occupational deterioration. Subtypes of schizophrenia are hebephrenic, catatonic, and paranoid. Initially, dementia was first described as a subtype of schizophrenia [3]. In several study, comparison were done between, familial schizophrenia (defined as an affected first-degree relative) and a group of sporadic schizophrenia cases but no difference in the intensity of depression, auditory hallucination, and delusion were noted. However, severe thought disorders were found more in the familial (57%) than of the sporadic (18%) patients with SCZ [4].

The patients with schizophrenia have extrapyramidal signs such as bradykinesia, rigidity or dyskinesias which is usually dopamine-receptor antagonists assigned to antipsychotic drugs.

Periodic catatonia which is a clinical subtype of schizophrenia, characterized by derangements of facial expression and gestures, known as psychomotor disturbances. Catatonia exhibit 2 psychotic ends, psychomotor excitement and inhibition. Including features- mask-like facies, iterations, and posture stereotypes, distorted stiff movements, or parakinesis, and akinetic negativism. Acute psychotic episodes may be accompanied by hallucinations and delusions, but, in remission, there remains a distinct mild to severe catatonic residual state with psychomotor weakness of facial expression and diminished incentive.

Schizophrenia and bipolar disorder are considered to be separate entities, but patients with multiple symptoms of both disorders are often given the hybrid diagnosis schizoaffective disorder [5]. The clinical features of these patients supported the argument that schizophrenia and bipolar disorder are variant expressions of a diathesis

There is abnormal epidermal growth factor (EGF) production in central and peripheral nerve tissues in patients with schizophrenia [6].

### **1.3. Risk factors**

There are several factors that contribute to the risk of developing schizophrenia.

#### **1.3.1. Genes and environment**

Several researches reported that schizophrenia sometimes runs in families. However, there are many people who have schizophrenia who don't have a family member with the disorder and conversely, many people with one or more family members with the disorder who do not develop it themselves. There are many different genes may increase the risk of schizophrenia, but the single gene dose not causes the disorder by itself. It is not yet possible to use genetic information to predict the development of schizophrenia. The interactions between genes and aspects of the individual's environment are necessary for the development of schizophrenia. Environmental factors may involve- exposure to viruses, malnutrition before birth, problems during birth, psychosocial factors.

#### **1.3.2. Different brain chemistry and structure**

An imbalance in the complex, interrelated chemical reactions of the brain involving the neurotransmitters mainly dopamine and glutamate plays an important role in schizophrenia and problems during brain development before birth lead to defective connections. The brain also undergoes major changes during puberty, and these changes could trigger psychotic symptoms in people who are vulnerable due to genetics or brain differences.

## **2. Genetic aspects of the disease**

### **2.1. Inheritance**

The pattern of inheritance of Schizophrenia is autosomal dominant (AD). It has a significant genetic component and the relatives risk in patient with SCZ is higher than that to relatives of controls and the recurrence risk ratio for monozygotic twins, 1<sup>st</sup> degree, 2<sup>nd</sup> degree, 3<sup>rd</sup> degree relatives were 48, 11, 4.25 and 2 respectively [7]. The average concordance rates for monozygotic and dizygotic twins were 46% and 14% respectively in their families.

Schizophrenia is a polygenic and multifactorial disorder, therefore, this do not have simple monomeric genetic determination. An assembly of genes involve in the progression of this disorder in AD manner (Table 1) [8]. Within the larger group, there may be entities that behave in a simple mendelian manner. Heston [8] pointed out that the definition of schizophrenia used by researchers is a broad one encompassing the schizoid state and the schizophrenic spectrum. Schizoid disease and schizophrenia occur with about equal frequency among the cotwins of

schizophrenic monozygotic twin probands, bringing the concordance rate near to 100%. About 45% of sibs, parents, and offspring of schizophrenics have schizoid disease or schizophrenia. About 4% of the general population is affected with schizoid-schizophrenic disease.

**Table 1:** Major gene involved in Schizophrenic disorder

Gene/Locus	Location	Inheritance pattern	Gene/Locus	Location
APOL2	22q12.3	Autosomal Dominant (AD)	SCZD6	8p21
APOL4	22q12.3		SCZD5	6q13-q26
RTN4R	22q11.21		SCZD3	6p23
COMT	22q11.21		SCZD1	5q23-q35
SCZD8	18p		DRD3	3q13.31
AKT1	14q32.33		SYN2	3p25.2
DAOA	13q33.2		DISC2	1q42.2
SCZD7	13q32		DISC1	1q42.2
HTR2A	13q14.2		CHI3L1	1q32.1
DAO	12q24.11		MTHFR	1p36.22
SCZD2	11q14-q21		SCZD12	1p36.2
SCZD11	10q22.3			

## 2.2. Molecular genetics

According to online updated database of schizophrenic genes (SzGene), out of 118 metaanalyses, a total of 24 genetic variants in 16 different genes (*APOE*, *COMT*, *DRD2*, *DRD4*, *GRIN2B*, *IL1B*, *MTHFR*, *SLC6A4*, *TPH1*, *DAO*, *DRD1*, *DTNBP1*, *GABRB2*, *HP*, *PLXNA2* and *TP53*) showed nominally significant effects with average summary odds ratios of approximately 1.23 [9]. According to proposed criteria for the assessment of cumulative evidence in genetic association studies, associations with variants in 4 of these genes, *DRD1*, *DTNBP1*, *MTHFR*, and *TPH1* were characterized as showing ‘strong’ epidemiologic credibility [10]. The SzGene database represents the first comprehensive online resource for systematically synthesized and graded evidence of genetic association studies in schizophrenia [9]. They noted that in their study 94, or 80%, of the SNPs in 45 genes showed no significant association with schizophrenia after all published case-control samples were metaanalyzed, either in the analyses combining all samples of all ancestries or across samples of European-only ancestry. The GWAS studies for schizophrenia and other psychiatric disorders have not been as successful as in other diseases or traits such as cancer, body mass, and height [11].

The de novo mutations, in *LAMA2*, *DPYD*, *TRRAP*, and *VPS39* affect genes with diverse functions and developmental profiles, but they also found a substantial contribution of mutations in genes with higher expression in early fetal life [12].

### 2.2.1. Association with *MTHFR* gene at chromosome 1p36

A number of experiments were performed to observe the genetic association of methylenetetrahydrofolate reductase gene (MTHFR), homocysteine level and risk of schizophrenia. Elevated homocysteine levels [13] and the TT genotype [13,14] were associated with increased risk of schizophrenia (Table 2).

### **2.2.2. Association with *NOS1AP* gene at chromosome 1q23**

If SCZ susceptibility genes (like *NOS1AP*) are present at 1q location, their population-wide genetic effects are likely to be small [15]. The A allele of rs12742393 (SNP of *NOS1AP* gene), a risk allele, is associated with schizophrenia that acts by enhancing transcription factor binding and increasing gene expression [16] (Table 2).

### **2.2.3. *CHI3L1* gene association at chromosome 1q32**

*CHI3L1* as a potential schizophrenia susceptibility gene and suggested that the genes involved in the biologic response to adverse environmental conditions are likely to play roles in the predisposition to schizophrenia [17] (Table 2).

### **2.2.4. Association with *DISC1* gene at chromosome 1q42**

A case-control study of a North American white population, confirming the underrepresentation of the HEP3 haplotype in individuals with schizoaffective disorder. Multiple haplotypes contained within 4 haplotype blocks extending between exon 1 and exon 9 were associated with SCZ, schizoaffective disorder and bipolar disorder [18] (Table 2). The other finding of the study was the overrepresentation of a missense allele of the *DISC1* gene, leu607 to pro, in schizoaffective disorder [18] (Table 2). These data supported the idea that these apparently distinct disorders have at least a partially convergent etiology and that variation at the *DISC1* locus predisposes individuals to a variety of psychiatric disorders.

### **2.2.5. *SYN2* gene association at chromosome 3p25**

In a study, a positive association of synapsin II was reported with SCZ in a case-control study [19] (Table 2). To analyze false-positive results in the presence of minor degrees of population stratification, another study was performed in Han Chinese probands and their parents by use of analyses of transmission/disequilibrium for 3 insertion/deletion (in/del) markers and 3 SNPs in the *SYN2* gene on chromosome 3p25 [19] (Table 2). A positive association was observed for rs2307981, rs2308169, rs308963, rs795009 and rs2307973. For transmission of 6-marker haplotypes, a global p value of high significance was found. This confirmed the previous study and provided further support for the role of synapsin II variants in susceptibility to SCZ.

### **2.2.6. *PMX2B* gene association at chromosome 4p13**

Authors was found a subtype of strabismus (ocular misalignment), constant exotropia, displayed marked association with SCZ ( $p < 0.01$ ) in a study [20] (Table 2). They identified frequent deletion/insertion polymorphisms in the 20-alanine homopolymer stretch of the transcription factor gene PMX2B, located on chromosome 4p13, with a modest association between these functional polymorphisms and constant exotropia in SCZ as compared to control samples ( $p > 0.01$ ) [20] (Table 2). The polymorphisms were also associated with overall SCZ ( $p = 0.012$ ) and more specifically with SCZ manifesting strabismus ( $p < 0.01$ ). These results highlight a possible interaction between PMX2B and other SCZ-precipitating factors and increasing the risk of the combined phenotypes.

### **2.2.7. DRD1 gene association with chromosome 5q35.1**

A meta-analysis was performed including 725 patients with schizophrenia with 1,075 controls and found that the DRD1 -48A-G allele (rs4532) was associated with susceptibility to SCZ (odds ratio, 1.18; 95% CI, 1.01-1.38;  $p = 0.037$ ) [9] (Table 2). As per Venice guidelines for the assessment of cumulative evidence in genetic association studies [10], the DRD1 association showed a strong degree of epidemiologic credibility.

### **2.2.8. ABCA13 gene association with chromosome 7p12.3**

ABCA13 is a susceptibility factor for both schizophrenia and bipolar disorder [21] (Table 2). Knight et al. 2009 [21] resequenced ABCA13 exons in 100 cases with schizophrenia and 100 controls. Multiple rare coding variants were identified including 1 nonsense and 9 missense mutations and compound heterozygosity/homozygosity in 6 cases. They also genotyped affected and unaffected relatives and found significant linkage ( $\text{lod}=4.3$ ) of rare variants with a phenotype including schizophrenia, bipolar disorder, and major depression [21]. They concluded that their data identified a candidate gene (*ABCA13*), highlighted the genetic overlap between schizophrenia, bipolar disorder & depression, and suggested that rare coding variants contribute significantly to these disorders.

### **2.2.9. Association with TPH1 gene at chromosome 11p15.3-p14**

A metaanalysis was performed comparing 829 patients with SCZ with 1,268 controls across all ancestries and found that the TPH1 A vs. C allele at position 218 in intron 7 (rs1800532) of the TPH1 gene was associated with susceptibility to schizophrenia [9] (Table 2). Therefore, TPH1 association showed a strong degree of epidemiologic credibility [10].

### **2.2.10. Association with BDNF gene at chromosome 11p13**

A group of scientist studied the *BDNF* gene as a risk factor for schizophrenia in a Scottish population that included 321 probands with a diagnosis of schizophrenia or schizoaffective disorder, 263 probands with a diagnosis of bipolar affective disorder and 350 controls [22]

(Table 2). The val66-to-met polymorphism showed significant ( $p < 0.01$ ) association for valine (allele G) with schizophrenia but not bipolar disorder [22] (Table 2). Haplotype analysis of the val/met SNP and a dinucleotide repeat polymorphism in the promoter region revealed highly significant ( $p < 0.01$ ) underrepresentation of the methionine (met1) haplotype in the schizophrenic but not the bipolar population. Therefore, the risk of this polymorphism depend upon haplotypic background on which the val/met variant is carried.

### **2.2.11. Association with the *YWHAE* gene on chromosome 17p13**

In a study, including 1,429 Japanese patients with SCZ and 1,728 controls, it was found that a significant association between a G-to-C SNP (rs28365859) in the 5' flanking region of the *YWHAE* gene [23] (Table 2). In vitro functional expression studies showed that the minor C allele was associated with higher gene expression and *YWHAE* mRNA and protein levels were higher in peripheral blood samples of C allele carriers compared to G allele carriers. An odds ratio of 0.76 was associated with the C allele, suggesting a protective effect [23] (Table 2). The heterozygous *YWHAE* mice had weak defects in working memory and increased anxiety-like behavior. Overall, the findings suggested that *YWHAE* may be a susceptibility gene for SCZ [23].

### **2.2.12. Association with the *APOE* Gene on Chromosome 19q13**

In a study of apolipoprotein E genotypes in patients with SCZ coming to autopsy, finding highlights that schizophrenia is associated with an increased E4 allele frequency [24] (Table 2).

### **2.2.13. Association with the *OLIG2* Gene on Chromosome 21q22**

An association between SCZ and several SNPs in the *OLIG2* gene (including rs1059004 and rs762178) was observed in Caucasian [25] and Chinese Han patients [26] (Table 2).

### **2.2.14. *COMT* gene association at Chromosome 22q11**

A case-control haplotype analysis was performed in catechol-O-methyltransferase (*COMT*) gene, the outcome of the study was a highly significant association between schizophrenia and a *COMT* haplotype ( $p = 9.5 \times 10^{-8}$ ) [27] (Table 2). Similarly, a large-scale association study was performed with a metaanalysis of the *COMT* val/met polymorphism and risk of schizophrenia in 862 patients and 928 healthy control subjects from a Han Chinese population [28] (Table 2). The metaanalysis provided no significant evidence for an association between schizophrenia and the val allele in Asian or European populations.

### **2.2.15. Association with the *PRODH* Gene on Chromosome 22q11**

In a study, authors analyzed the *PRODH* gene in patients with SCZ and their families



from Sichuan Province in China, comprising 528 family trios and sib pairs [29] (Table 2). They found association of SCZ with 2 haplotypes consisting of the 1945T-C and 1852G-A variants (global  $p = <0.01$ ) and the 1852G-A and 1766A-G variants (global  $p=0.01$ ).

### 2.2.16. Association with CAG/CTG Repeats

In a study, a repeat expansion detection assay was used to examine genomic DNA from 100 unrelated probands with SCZ and 68 unrelated probands with bipolar affective disorder for the presence of CAG/CTG repeat expansions [30]. Study found that 28% of probands with SCZ and 38% of probands with bipolar disorder had CAG/CTG repeats in the expanded range.

**Table 2:** Summary of the supporting evidence for SCZ susceptible region

Study providing support	Population studied	Study	Statistical evidence	Region/Gene
Allen <i>et al.</i> 2008	U.S. (Afro-American)	Meta-analysis	OR= 1.23	Multigenic
Ioannidis <i>et al.</i> 2008	-	-		Multigenic
Sullivan <i>et al.</i> 2010	-	GWAS		
Xu <i>et al.</i> 2012	African-US	Case-control		Multigenic
Muntjewerff <i>et al.</i> 2005	Dutch	Case-control	OR= 3.3	1p36/ <i>MTHFR</i>
Lewis <i>et al.</i> 2005	-	Meta-analysis	OR= 1.48	1p36/ <i>MTHFR</i>
Levinson <i>et al.</i> 2002	Multicentre	Genotyping		1q23/ <i>NOS1AP</i>
Wratten <i>et al.</i> 2009	Canadian	Genome wide scan		1q23/ <i>NOS1AP</i>
Zhao <i>et al.</i> 2007	Chinese	Case-control		1q32/ <i>CHI3L1</i>
Hodgkinson <i>et al.</i> 2004	North-America	Case-control		1q42/ <i>DISC1</i>
Chen <i>et al.</i> 2004	Han Chinese	Case-control	$p < 0.01$	3p25/ <i>SYN2</i>
Toyota <i>et al.</i> 2004	-	Case-control	$p = 0.029$	4p13/ <i>PMX2B</i>
Knight <i>et al.</i> 2009		Case-control	lod= 4.3	7 p 1 2 . 3 / <i>ABCA13</i>
Neves-Pereira <i>et al.</i> 2005	Scottish	Case-control	$p = 0.005$ , $p < 0.00000001$	11p13/ <i>BDNF</i>
Ikeda <i>et al.</i> 2008	Japanese	Case-control	OR= 0.76	17p13/ <i>YWHAE</i>
Harrington <i>et al.</i> 1995	-	Genotyping		19q13/ <i>APOE</i>
Georgieva <i>et al.</i> 2006	Caucasian	Case		21q22/ <i>OLIG2</i>

Huang <i>et al.</i> 2008	Han Chinese	Case	p= 0.009	21q22/ <i>OLIG2</i>
Shifman <i>et al.</i> 2002	Ashkenazi Jews	Case-control	p= 9.5x10 <sup>-8</sup>	22q11/ <i>COMT</i>
Fan <i>et al.</i> 2005	Han Chinese	Meta-analysis	OR=1.09	22q11/ <i>COMT</i>
Li <i>et al.</i> 2004	Chinese	Familial	p=0.006, p= 0.01	22q11/ <i>PRODH</i>
Brzustowicz <i>et al.</i> 2000	Canadian	Genome wide scan	lod= 6.5	1 q 2 1 - q 2 2 / NOS1AP
Mirnicsa <i>et al.</i> 2001	Multicenter	Genome wide scan		1q/RGS4
Gurling <i>et al.</i> 2001	Iceland/UK	-	MLS¼3.2	8p22.1–22
Hovatta <i>et al.</i> 1999	Finland (isolate)	-	Zmax¼3.8	1q32.2–q41

### 3. Pathogenesis of the disease

The pathophysiology of SCZ shared features with other neurodevelopmental disorders. A diverse group of network, related components, various gene etiology and several other factors involve in the pathogenesis of SCZ.

The environmental factors do not significantly contribute to the pathogenesis of schizophrenia [31]. Some forms of schizophrenia associated with latitude, urban birth, household crowding, having older sibs, and famine during pregnancy [32]. Exposure of certain drugs (DSM-IV) responsible for similar syndromes.

Schizophrenia symptoms is associated with functional and structural changes in neocortical regions (prefrontal and temporal-cortices and their connections and integrative interactions) and cortical regions. Genetic load, adverse embryonic and perinatal events responsible for neurodevelopmental first hit that leads to schizophrenic vulnerability. The most frequent embryonic and perinatal factors include viral illness during the 2<sup>nd</sup> trimester of pregnancy, low birth weight, short gestational period and perinatal brain damage. Hormonal events (as altered neurosteroid biosynthesis) act as a second hit which facilitate excitotoxicity or oxygen radical formation owing to environmental factor [33].

Apolipoproteins (APOL2 and APOL4), found in cortical region of brain, were significantly upregulated in schizophrenia [34]. The APOL proteins is high density lipoproteins. and all 6 APOL genes are located in close proximity to each other on chromosome 22q12 which is a high-susceptible locus for schizophrenia (SCZD4) and close to velocardiofacial syndrome region which includes symptoms of schizophrenia. The high density lipoprotein plays a central role in cholesterol transport. The cholesterol content of membranes is important in cellular processes (gene transcription and signal transduction) and during neurodevelopment.

The AKT1/GSK3B signaling pathway has significant role in schizophrenia. The de-

crease in protein levels of AKT1 and phosphorylation of GSK3B at ser9 in the peripheral lymphocytes and brains of schizophrenia patient [35]. Similarly, the gene encoding phosphodiesterase 4B (PDE4B) is disrupted by a balanced translocation in schizophrenia. The phosphodiesterases inactivate cAMP (secondary messenger) which is involved in learning, memory and mood. The DISC1 gene interacts with the UCR2 domain of PDE4B and that elevation of cellular cAMP leads to dissociation of PDE4B from DISC1 and in increase in PDE4B activity [36].

A nonprotein coding RNA (ncRNA) plays a critical role in regulating the timing and rate of protein translation, therefore possibility ncRNA regulation of genes by ncRNA may account for the diverse findings of genetic linkage and association studies for schizophrenia [37].

In SCZ, human induced pluripotent stem cells (hiPSC) neurons showed diminished neuronal connectivity in conjunction with decreased neurite number, PSD95 protein levels and glutamate receptor expression [38]. Gene expression profiles of SCZ hiPSC neurons identified altered expression of many components of the cAMP and WNT signaling pathways. Therefore, SCZ phenotypes were ameliorated by treatment of Schizophrenic hiPSC neurons with the antipsychotic loxapine.

#### **4. Diagnosis**

The appropriate choice of diagnostic criteria for SCZ is difficult due to overlapping of several neurodegenerative & neurodevelopmental disorders (schizoaffective, schizotypal, schizophreniform and delusional disorders) and personality disorders such as schizoid schizotypal and paranoid [39,40]. However, interrater reliability for the diagnosis of SCZ is excellent, with estimates of kappa ranging from 0.76 to 0.82 and measurements of test-retest reliability from 0.68 to 0.7.

Diagnosis of SCZ involves ruling out other mental health disorders and determining that symptoms are not due to substance abuse, medication or a medical condition. A specific DSM guideline is used in the appropriate diagnosis of SCZ by experts. Diagnosis of schizophrenia include-

##### **4.1. Physical and psychiatric evaluation**

Physical examination involve in the ruling out other problems that could be causing symptoms and to check for any related complications. There are several examples of other etiologies presenting with similar symptomatology:

- A blank, vacant facial expression: An inability to smile or express emotion through the face is so characteristic of the disease that it was given the name of affective flattening or a blunt affect.

- Clumsy, inexact motor skills
- Sleep disturbances- insomnia or excessive sleeping
- Overly acute senses- lights are too bright, sounds are too loud.
- Staring, while in deep thought, with infrequent blinking.
- Involuntary movements of the tongue or mouth (facial dyskinesias). Grimacing at the corners of the mouth with the facial muscles, or odd movements with the tongue.
- An awkward gait (how you walk)
- Eye movements- difficulty focusing on slow moving objects
- Unusual gestures or postures
- Movement is speeded up- i.e. constant pacing
- Movement is slowed down- staying in bed (in extreme cases, catatonia)
- Parkinsonian type symptoms- rigidity, tremor, jerking arm movements, or involuntary movements of the limbs.

On the other side, psychiatric professional checks mental status by observing appearance and demeanor and asking about thoughts, moods, delusions, hallucinations, substance use and potential for violence or suicide.

## 4.2. Clinical testing and screening

This includes tests that rule out conditions with similar symptoms and screening for alcohol & drugs. Specific blood tests, MRI and/or CT scan are also recommended to point out the sign and symptoms associated with SCZ and overlapping disorder.

## 4.3. Molecular diagnosis

The clinical presentation and course of SCZ is highly variable and the evidence of fundamental genetic heterogeneity or division into genetic and nongenetic forms is minimal. Therefore, further developments will depend on the application of molecular genetic marker strategies and on the discovery of endophenotypes [41].

The increased D3 dopamine receptor (DRD3) mRNA on blood lymphocytes is a useful bio-marker for identification and follow-up of schizophrenia [42]. Similarly, Eye movement disturbances act as a phenotypic marker for schizophrenia [43,44]. An association between eye movement disturbances and ser9 polymorphism in the *DRD3* gene was found. Thus, DRD3 polymorphism acts as a contributing factor to the eye movement disturbances in SCZ.

## 5. Management and therapeutics

Coping with a mental disorder such as schizophrenia is challenging for both the person with the condition and for friends & family. Some ways to cope are- learn about SCZ, join a support group, stay focused on goals, learn relaxation and stress management, ask about social services assistance, and others.

SCZ requires lifelong treatment, even when symptoms have subsided. Treatment with medications and psychosocial therapy help in managing the condition. The SCZ treatment modality include:

## **5.1. Medication**

Medications are the cornerstone of SCZ treatment, and antipsychotic medications are the most commonly prescribed drugs. They control symptoms by affecting the brain neurotransmitter dopamine. The goal of treatment with antipsychotic medications is to effectively manage signs and symptoms at the lowest possible dose. The psychiatrist may try different drugs, different doses or combinations over time to achieve the desired result. Other medications like as antidepressants or anti-anxiety drugs also help. It takes 1 week for response to occur (NICE, UK). SCZ medications can cause serious side effects so schizophrenic may be reluctant to take them. There could be many reasons for refusal to take medications-eg. lack of insight. Impaired insight often reflects obliviousness to one's condition, mirroring anosognosia in neurological disorders [45,46]. The use of denial coping strategies, on the other hand is more sophisticated, and necessitates some initial awareness of a condition that one then actively ignores and rebuffs.

### **5.1.1. First-generation antipsychotics**

These first-generation antipsychotics have frequent and potentially significant neurological side effects, including the possibility of developing a movement disorder (tardive dyskinesia) that may or may not be reversible. First-generation antipsychotics include: Chlorpromazine, Fluphenazine, Haloperidol, Perphenazine

### **5.1.2. Second-generation antipsychotics**

These newer, second-generation medications are generally preferred because they pose a lower risk of serious side effects than do first-generation antipsychotics. SCZ is treated chiefly with dopamine antagonists. Atypical antipsychotic drugs (2<sup>nd</sup> generation) has been used to avoid extra pyramidal side effects resulting from prolonged use of dopamine antagonists. Second-generation antipsychotics include- Aripiprazole (Abilify), Asenapine (Saphris), Brexpiprazole (Rexulti), Clozapine (Clozaril), Olanzapine (Zyprexa). Paliperidone (Invega), Quetiapine (Seroquel), Risperidone (Risperdal), Ziprasidone (Geodon) etc.

Clozapine and olanzapine use appears to be associated with greatest risk of metabolic

syndrome; iloperidone, quetiapine, risperidone, paliperidone, sertindole and zotepine are associated with intermediate risk; while amisulpride, aripiprazole, asenapine, lurasidone and ziprasidone are associated with only a small increase in risk [47,48]. The increased risk of diabetes was identical in users of olanzapine, quetiapine and risperidone [49]. No antipsychotic is completely free of metabolic side effects [50]; even those usually without such effects may cause them in specific situations. Thus, although aripiprazole does not increase body weight in adults, weight gain has been reported in paediatric patients following aripiprazole administration [51,52]. Furthermore, long-term side effects tend to come to light only after a drug has been on the market for some time [53], and most data on the side effects of antipsychotics have been obtained from trials on patients with many years of prior drug exposure, and this could lead to the underestimation of side effects in the more recently introduced antipsychotics such as aripiprazole, asenapine, lurasidone and ziprasidone [54]. Finally, metabolic alterations appear to be an intrinsic effect of antipsychotics, since they appear when these drugs are employed to treat diseases other than schizophrenia [55,56].

Second generation antipsychotics prolong the electrocardiogram QT interval and this has been identified as an important trigger for torsades de pointes, a transient and unpredictable form of polymorphic ventricular tachycardia [57]. Cardiac dopamine-2 receptor blockade by 2<sup>nd</sup> generation antipsychotics is responsible for the increased sudden deaths, due to cardiac arrhythmias.

## **5.2. Psychosocial interventions**

Once psychosis recedes psychological and social (psychosocial) interventions are important. These may include:

### **5.2.1. Individual therapy**

Psychotherapy help to normalize thought patterns. Also, learning to cope with stress and identify early warning signs of relapse can help schizophrenic to manage their illness.

### **5.2.2. Social skills training**

This focuses on improving communication and social interactions and improving the ability to participate in daily activities.

### **5.2.3. Family therapy**

This provides support and education to families dealing with SCZ.

### **5.2.4. Vocational rehabilitation and supported employment**

This focuses on helping people with SCZ prepare for finding and to keep jobs. Most

schizophrenic require some form of daily living support. Many communities have programs to help people with schizophrenia with jobs, housing, self-help groups and crisis situations.

### 5.3. Electroconvulsive therapy

Schizophrenic adults (not responding towards drug therapy), have been provided electroconvulsive therapy (ECT). ECT may be helpful for someone who also has depression.

## 6. Summary, conclusion and future prospective

SCZ is a severe mental disorder in which people interpret reality abnormally. It may result in some combination of hallucinations, delusions, and extremely disordered thinking and behavior that impairs daily functioning, and can be disabling. A assembly of network and related system etiologies impart role in pathophysiology of SCZ. The appropriate choice of diagnostic criteria for SCZ is difficult owing to overlapping features with other related disorders. It is a chronic condition and thus requires lifelong treatment because there is no sure way to prevent SCZ. However, early treatment may help get symptoms under control before serious complications develop and may help improve the long-term outlook. Sticking with the treatment plan can help prevent relapses or worsening of schizophrenia symptoms. In addition, researchers hope that learning more about risk factors for SCZ may lead to earlier diagnosis and treatment.

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