



Review Article

## Dimensions of Schizophrenia; Existence A Boon to Therapeutic Interventions

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### ABSTRACT

Dimension classification is a quantification of phenomenology that is distributed continuously without boundaries and subjects with higher ordinal scores indicate presence of disorder. Historically existence of dimensions of schizophrenia was observed right from its conceptualization based on etiopathology, natural progression of illness. Failure of two dimensional approaches by Hughlings-jackson, Kay and Opler to describe all symptoms of schizophrenia, Bilder and Liddle proposed three cluster/symptom dimensions using principal component analysis and factor analysis respectively. Gay and kay et al. proposed five factor dimensions derived from BPRS and PANSS scale respectively. Large scale research studies on five factor derived dimensions using conventional and atypical antipsychotic drugs have underpinned the neurobiological cause for occurrence of various dimensions (specifically positive, negative and cognitive dimension) prompting researchers for development of newer drugs targeting excito-toxic effects of free radical production. Mcgrath and colleagues studied genetic basis of nine factor derived dimension that tie together various signs and symptoms of schizophrenia. Nine dimensions explained 35 % variance; ratio of polygenic variance to total variance as a measured of heritability showed all nine factors running in families. Disability/impairment highest heritability factor (0.61) followed by disorganization 0.60). Later genetic studies identified disorganization one of most familial factor showing clear evidence of genetic influence. Identification of these factor scores as phenotypes in quantitative trait locus linkage and association studies. Disorganization and disability which is debilitating outcome of chronic schizophrenia, definitive identification of neurobiological cause and genetic trait locus helps in discovery of newer drugs and early intervention.

**Key words:** dimensions, disorganization, negative symptoms, positive symptoms, schizophrenia,

### INTRODUCTION

Dimensional system classifies clinical presentation based on quantification of attributes and works best in describing phenomenon that are distributed

continuously without clear boundaries. Schizophrenia is a disorder with constellation of symptoms and categorized into various subtypes based on grouping of different symptoms. <sup>[1]</sup>

Categorization is unable to explain the etiology, progression, disability and symptom changes with therapeutic intervention. Hence there were several attempts to group these symptoms along meaningful dimensions. Initially a three dimensional approach was proposed. [2,3] Later, studies have consistently found the presence of at least five factor derived dimensions. Genetic studies have identified nine factor derived dimensions running in families. [4-7]

Studies have found that each dimension showing the set pattern response to different class of antipsychotics supporting the existence of dimensions in schizophrenia.

This article attempts to look into evolution of dimensional concept of schizophrenia supported by various research studies using various classes of antipsychotics and genetic studies.

#### **Dimensional Concept of schizophrenia**

Categorical and dimensional concepts of schizophrenia have varied considerably from time to time and from place to place. The weightage given to these concepts has differed from time to time and person to person.

The historical developments of the concept of schizophrenia started as early as eighteenth century. To begin with, all the mental disorders were considered as expressions of single entity, which Griesinger called *Einheit Psychose* (unitary psychosis). [8]

Later people started viewing mental disorders as constellation of different entities, which could be separated and classified. In 1852 Morel, argued for the classification based on the cause, symptoms, and outcome and he gave the name *de'mence pre'coce* (disorder starting in adolescence and leading first to withdrawal, odd mannerisms, and self-neglect, and eventually to intellectual deterioration). Not

long after, Kahlbaum in 1863 described the syndrome of "*catatonia*" and Hecker in 1871 wrote an account of a condition, which he called "*hebephrenia*". [9,10]

In late nineteenth century and early part of twentieth century based on the specific observations on the symptoms and clinical course, attempts were made to conceptualize schizophrenia. Following are some of the works which provide insight in to the evolution of different aspects of schizophrenia.

#### **Concepts of Emil Kraepelin (1855 –1926) [11]**

Emil Kraepelin argued against the idea of unitary psychosis based on the observations made on the course of the disorder. He categorized mental disorder (Kraepelinian dichotomy) into dementia praecox and manic-depressive psychosis. Kraepelin described dementia praecox as illness occurring in clear consciousness and consisting of 'a series of states'. The common characteristic of which is a "destruction of the internal connections of the psychic personality". The effects of this injury predominate in the emotional and volitional spheres of mental life.

He originally divided the disorder into three subtypes; Catatonic, Hebephrenic and Paranoid and later added a fourth; Simple. Kraepelin separated paraphrenia from dementia praecox on the grounds that it started in middle life and seemed to be free from the changes in emotion and volition found in dementia Praecox.

#### **Concepts of Eugen Bleuler (1857-1859) [12]**

Eugen Bleuler based his work on that of Kraepelin and with the help of Karl Gustav Jung applied some of Freud's ideas to dementia praecox. Bleuler was concerned less with prognosis and more with the mechanisms of symptom formation. It was Bleuler who proposed the name Schizophrenia to denote a splitting of

psychic functions, which he thought to be of central importance.

Bleuler believed in a distinction between Fundamental and Accessory symptoms. Fundamental symptoms included disturbances of associations, changes in emotional reactions and autism (withdrawal from reality into an inner world of fantasy). It is interesting that in Bleuler's view some of the most frequent and striking symptoms (hallucinations, delusions, catatonia and abnormal behaviors) were accessory (secondary). Bleuler was interested in the psychological study of his cases but did not deny the possibility of neuropathological causes for schizophrenia. Compared with Kraepelin, Bleuler took a more optimistic view of the outcome, but still held that one shouldn't speak of cure but of far reaching improvement. He also wrote; "As yet I have released a schizophrenic in whom I couldn't still see distinct signs of a disease, indeed there are very few in whom one would have to search for such signs". Since Bleuler was preoccupied more with psychopathological mechanisms than with symptoms themselves, his approach to diagnosis was less precise than that of Kraepelin.

#### **Kurt Schneider Concepts of First Rank symptoms (1887-1967) [13]**

Kurt Schneider tried to make the diagnosis more reliable by identifying a group of symptoms characteristic of schizophrenia, rarely found in other disorders. Thus Schneider found that among the many abnormal modes of experience that occur in schizophrenia, there are some which he put in the first rank of importance, not because he thought of them as basic disturbances but because they have this special value in helping us to determine the diagnosis of schizophrenia. When any one of these modes of experience is undeniably present and no basic illness can be found, we may make the diagnosis of

schizophrenia (Hearing thoughts spoken aloud, third person auditory hallucination in the form of commentary, somatic hallucination, thought withdrawal or insertion, thought broadcasting, delusional perception, feelings or action experienced as made or influenced by external agents).

#### **Concepts of Leonhard (1957) [14]**

Leonhard based on careful clinical observation published a complicated classification, which distinguishes schizophrenia from the cycloid psychoses. He grouped them under non-affective psychoses with good outcome.

Leonhard also divided schizophrenia into two groups Systematic and Non-systematic. The first group is characterized by a progressive course, and is divided into catatonias, hebephrenias and paraphrenia. The second group, called non-systematic which is divided into affect-laden paraphrenia characterized by paranoid delusions and expression of strong emotions about their content and schizophasia (speech is grossly disordered and difficult to understand) and periodic catatonia with regular remission, during an episode akinetic symptoms are some time interruptive by hyper-kinetic symptoms.

With increased heterogeneous concept of schizophrenia Leonhard's views of three forms of cycloid psychosis (anxiety elation psychosis, confusion psychosis, and motility psychosis) were much accomplished and later considered as bipolar disorders having good prognosis and leaving no chronic defect state. This concept has promoted many researchers in recent times to look into existence of dimensions in affective disorder in parallel with schizophrenia.

#### **Crow et al (1982) [15]**

Crow and his colleagues described two syndromes to standardize diagnostic criteria. Type I schizophrenia, which is of acute course, reversible, increase in

dopamine receptors, and presence of positive symptoms (Hallucinations and delusions, and thought disorder) may be treatable by drugs. Type II schizophrenia characterized by chronic course, irreversible with subtle loss of brain tissue and presence of negative symptoms (alogia, affective flattening, anhedonia, asociality, avolition-apathy and attention impairment) may have poor response to drugs.

With origin of wide range of concepts of schizophrenia there were divergences in the criteria for diagnosis of schizophrenia. The concept of dimension started with grouping of the commonly occurring symptoms.

**Griesinger** was the first person to introduce the concept of primary and secondary symptoms in a temporal sense, where primary was used to denote depression that appeared first and secondary for dementia that appeared later. **Gruhle** used primary to mean final and irreducible. Further **Brinbaum** used Primary and secondary to mean pathogenic and pathoplastic respectively. In 1911, **Bleuler** in parallel with fundamental and accessory symptoms introduced concept of primary where he made a distinction saying that primary is caused by disturbance in association and secondary symptoms are a direct consequence of the loosening of association. In 1957 **Schneider** came up with concept of first rank symptoms (Symptoms of special value which help to make diagnosis) and later by **Crow et al** type I and type II schizophrenia with presence of positive and negative symptoms respectively. [8,15,16]

In summary, reorganizing of various symptoms into different dimensions is to find etiopathological basis, monitoring the natural progression of disease and course of illness with therapeutic intervention. Several attempts have been made to group the numerous symptoms of schizophrenia into

meaningful dimensions. Several dimensions have been proposed as reviewed below.

### **Two-dimensional approach**

Hughlings-Jackson, a nineteenth century neurologist was the earliest to provide us comprehensive discussion of positive and negative symptoms although Reynolds had made an earlier but less extensive presentation. Hughlings-Jackson applied two-dimensional model to the understanding of various syndromes, including the psychoses. He suggested that positive symptoms such as delusions or hallucinations represented release phenomena; they were symptoms arising when a higher cortical regulator or organizer had been lost and the activity from a lower level therefore emerged unchecked. Similarly Negative symptoms, such as avolition or emotional blunting, were due to dissolution that is they represented a diffuse or generalized loss of regulator mechanism at higher centers. [17,18]

On the same model of Hughlings, Kay and Opler proposed the presence of *neuroleptic responsive arousal-related dimension* called as positive dimension and *Neuroleptic resistant development-related dimension* as negative dimension. They emphasized the prevalence of these dimensions in both acute and chronic schizophrenia. However, these dimensions become more stable only in chronic schizophrenia. [19]

### **Three dimensions**

Researchers consistently found the two-dimensional approach to be insufficient to describe all symptoms of schizophrenia. Bilder and colleagues were the first to find three clusters using principal component analysis into which the symptoms of schizophrenia could be grouped. [20]

- a. First cluster of symptoms reflected **disorganization of thought; alogia, attentional impairment, positive**

*formal thought disorder, and bizarre behavior*

- b. Second cluster of symptoms reflected **blunting of affect and volition**; *affective flattening, avolition/apathy, and anhedonia*
- c. Third cluster represented florid psychotic features; *delusions, hallucinations, and "breadth of psychosis"*

The symptom clusters were derived from Schedule for Affective Disorders and Schizophrenia (SADS) and Scale for the Assessment of Negative Symptoms (SANS). [21,22]

Liddle later proposed the presence of three symptom dimensions in chronic schizophrenia on similar lines: using factor analysis of symptoms of schizophrenia derived using items from comprehensive Assessment of Symptoms and History (CASH) and Present Status Examination (PSE). [23,24]

- a. Disorganization
- b. Psychomotor poverty
- c. Reality distortion

Later several studies found similar results, that at a descriptive level, three dimensions are required to account for interrelationships among symptoms of schizophrenia, as reviewed by Andreasen et al; Psychosis dimension, disorganization dimension and negative symptoms. [3]

### **Five dimensions**

Guy et al suggested five factor-derived dimensions using BPRS. [25] Van Os et al; Vander Does et al and Kay & Sevy reported presence of domains such as excitation/activation, insight or awareness of illness, and depression. [26-28]

Kay et al developed Positive and Negative Syndrome Scale (PANSS) using items from Brief Psychiatric Rating Scale (BPRS) and Psychopathology Rating Scale. The items are selected based on five

guidelines in the following order of importance. [19,29]

- a) Items must be consistent with theoretical concept of positive and Negative psychopathology as representing productive features superadded to the mental status versus deficit features characterized by loss of functions.
- b) They should comprise symptoms that can be unambiguously classified as positive or negative and which by most accounts are regarded as primary rather than derivative.
- c) They should include symptoms that are consensually regarded as central to the definition of positive syndrome (hallucinations, delusions, and disorganized thinking) and negative syndrome (blunted affect, emotional withdrawal and impoverished communication).
- d) To optimize content validity they should sample from diverse realms of functioning, such as the cognitive, affective, social and communications; and
- e) For practical and psychosomatic reasons such as facilitating across comparisons and equalizing reliability potential, the number of items in the positive and negative scales should be the same.

Studies using PANSS have consistently found the presence of five factor dimensions in Schizophrenic symptomatology, as reviewed below.

PANSS scale has been used extensively in most research studies of schizophrenia, especially those examining the effect of treatment modalities in schizophrenia. Because the PANSS was developed as a refinement and extension of the Brief Psychiatric Rating Scale (BPRS), items may be similarly combined and scored for the five factors derived dimensions obtained with the BPRS Viz. anergia, thought disturbance, activation, paranoid-belligerence, and depression.

Studies using PANSS as well as a re-analysis of the original sample of Kay and

Sevy, favour a five-factor solution: negative, positive, disorganized, excited and depression/anxiety factors. [30-34]

PANSS has seven positive (p1 to p7) and seven negative items (N1 to N7), in

addition 16 symptoms that cannot be linked decisively to either syndrome are included and comprise a general psychopathology scale (G1 to G16).

Positive And Negative Symptom Scale For Schizophrenia (PANSS)

POSITIVE SCALE	NEGITIVE SCALE	GENERAL PSYCHOPATHOLOGY	
P1 Delusion	N1 Blunted affect	G1 Somatic concern	G9 Unusual thought content
P2 Conceptual Disorganization	N2 Emotional withdrawal	G2 Anxiety	G10 Disorientation
P3 Hallucinatory behavior	N3 Poor rapport	G3 Guilt feeling	G11 Poor attention
P4 Excitement	N4 Passive apathy Social Withdrawal	G4 Tension	G12 Lack of judgment and insight
P5 Grandiosity	N5 Difficulty in Abstract thinking	G5 Mannerisms and posturing	G13 Disturbance of violation
P6 Suspiciousness	N6 Lack of Spontaneity	G6 Depression	G14 Poor impulse control
P7 Hostility	N7 Stereotyped thinking	G7 Motor retardation	G15 Preoccupation
		G8 Uncooperativeness	G16 Active social avoidance

General psychopathology and factor scores as reference points, or control measures, for interpreting the positive and negative syndrome scores

Positive syndrome = sum of P1 through P7

Negative syndrome = Sum of N1 through N7

Composite index = Positive Syndrome – Negative Syndrome

General Psychopathology = Sum of G1 through G16

Five factor scores are obtained by summing statistically related items; these factors are

- Anergia = N1+N2+G7+G10
- Thought disturbance=P2+P3+P5+G9
- Activation =P4+G4+G5
- Paranoid/ belligerence = P6+P7+G8
- Depression = G1+G2+G3+G6

### Nine Dimensions of Schizophrenia

Researchers argue that the complexity of schizophrenia is hampering the search for its causes, and that breaking the disorder down into more homogeneous parts, at the level of phenotypes or the even more basic level of endophenotypes, may speed progress. Identifying the dimensions that tie together various signs and symptoms of schizophrenia, include indicators of social functioning, occupational performance, and

prodromal features. The dimensions were found to cluster in families.

The “divide and conquer strategy” for finding the genes responsible for schizophrenia; involves dividing up the manifestations of the illness into related groupings and then seeking the genes that contribute to each grouping.

In tune with this thinking, McGrath and colleagues used factor analysis to unearth leads for genetic studies. [7] They argued that schizophrenia “is likely several related disorders with varying and sometimes overlapping genetic underpinnings, some of which affect clinical and course features.”

This view led them to examine an unusually broad set of schizophrenia manifestations. Specifically, they tested a set of seventy three items, which went beyond positive symptoms, negative symptoms, affect, and disorganized thoughts and behavior. They also included measures of disturbed social functioning during childhood and adolescence, social and occupational decline, and academic performance.

They examined 1,199 people who met criteria for schizophrenia or schizoaffective disorder across United

States, Canada and Europe. Information on each subject's signs, symptoms, and psychiatric history came from clinical interviews, medical records, and proxy reports. At least two diagnosticians reviewed the data to render consensus judgments regarding diagnoses and other key information.

The McGrath and associates recognized *nine dimensions* that explain 35 percent of the variance in their data. Whether these dimensions will speed the hunt for elusive schizophrenia genes depends, in part, on their heritability. Though study design did not test heritability per se, but was able to probe whether the factors they found clustered in families. They used a heritability measure, the ratio of polygenic variance to total variance, to gauge familiarity.

To map out family ties of the 1,199 subjects, the study used information on 553 of their family members. Most families (714) had only one member with schizophrenia, but 207 had more than one. The results hint that all of the nine factors run in families.

In particular, disability/impairment showed the highest heritability at 0.61, with disorganization coming in at a nearly identical at 0.60. Child and adolescent sociability showed the lowest at 0.27. Heritability for the other factors ranged from 0.36 to 0.53.

**Five of the factors** echo those in many other factor analytic studies of schizophrenia, including those tapping

- a. Hallucinations,
- b. Negative symptoms,
- c. Affective symptoms,
- d. Disorganization
- e. Schneiderian first-rank symptoms.

The last reflects signs and symptoms that psychiatrist Kurt Schneider (Schneider, 1974) considered central to schizophrenia, such as hearing one's thoughts broadcast to other people, attributing one's thoughts to

insertion by others, and other forms of delusions.

In addition, McGrath and colleagues report **four dimensions** that they describe as new to factor analytic studies in schizophrenia, although they mirror known features of schizophrenia.

- a. Disability/impairment factor (including highest loading items pertaining to work functioning)
- b. Scholastic factor (includes aspects of elementary, high school and college performance)
- c. Prodromal factor (encompasses warning signs, such as role impairment, avoidance of social interactions, odd behavior, and bizarre thoughts, which may precede full-blown schizophrenia.
- d. Social relations factor (Items related to childhood and adolescent sociability)

McGrath and colleagues reported depression and mania as one (affective) factor rather than separate due to its inclusion of relatively few mood items. Moreover affective factor correlated only weakly and inversely with the negative symptoms dimension, which suggests that they arise independently.

Rietkerk et al review of metaanalysis of genetic studies report evidence for genetic contributions to three dimensions—namely, *reality distortion* (hallucinations and delusions); *psychomotor poverty* (flat affect, scant speech, and decreased spontaneous movement); and *disorganization* (formal thought disorder, inappropriate affect, and strange behavior). Only *disorganization*, one of the most familial factors in the McGrath study, showed clear evidence of genetic influence. <sup>[35]</sup>

Having generated factors that they hoped would provide leads for genetic studies; the researchers are putting them to the test. They are now using the factor

scores as phenotypes in quantitative trait locus linkage and association studies

### **Neurobiological Basis of existence of dimensions of schizophrenia**

The biological basis of schizophrenia remains unknown. However, the monoamine neurotransmitter dopamine plays a key role in hypothesis about certain aspects of the five dimensions of symptoms in schizophrenia. [36]

To understand neurobiological basis of symptom dimension. Symptoms are categorized into five dimensions as follows: Positive, negative, cognitive, and aggressive/hostile, and depressive/anxious symptoms. [32]

- a. *Positive symptoms* where defined excess of normal functions like delusions, hallucinations, distortions or exaggeration in language and communication as well as behavioral monitoring (disorganized, catatonic or agitated).
- b. *Negative symptoms*: Defined as reduction in normal functions as affective flattening (restrictions in the range and intensity of emotional expression, alogia (restrictions in the fluency and productivity of thought and speech), avolition (restriction in the initiation of goal directed behavior), anhedonia (Lack of pleasure) and attention impairment. Negative symptoms in schizophrenia can be either primary or secondary. Primary are core to primary deficits of schizophrenia itself and secondary because of extra pyramidal symptoms due to antipsychotic use, depression or environmental deprivation [37-39]
- c. *Cognitive symptoms*: Include impaired verbal fluency, problems with serial learning, impairment in vigilance for executive functioning.

- d. *Aggressive and hostile symptoms*: Overlap with positive symptoms but specific problems in impulse control they include verbal or physical abusiveness or even assault, self-injurious behavior, sexual acting out behavior.
- e. *Depressive and anxious symptoms*: Depressed mood, anxious mood, guilt, tension, irritability and worry.

Neurobiological basis of positive symptoms

- a. Hyperactivity in Mesolimbic dopamine pathway projecting from dopaminergic cell bodies in ventral tegmental area of the brain, nucleus accumbens mediates positive symptoms. [40]
- b. Aberrant serotonergic control of dopamine results in hyperactivity of mesolimbic dopamine receptors causing impulse dyscontrol (aggression and hostile symptoms) in schizophrenia. [41]

### **Neurobiological basis of Negative and cognitive symptoms**

- a. Deficiency of dopamine in the mesocortical projections in the dorsolateral prefrontal cortex is believed to be causation of negative symptoms and certain cognitive symptoms. Dopamine deficit in the mesocortical area could be primarily due to inhibition, by an excess of serotonin in the pathway or secondary to the blockade of dopamine 2 receptors by antipsychotic drugs. [42,43]
- b. Burn out of neuronal systems, due to excitotoxic over activity of glutamate systems mediated or neurodegenerative process in schizophrenias. The mechanism of excitotoxicity is mediated by NMDA receptors. It triggers glutamate activity causing opening of calcium channels activating the intracellular

enzymes that form potentially dangerous free radicals. Free radicals with toxic actions on cellular membranes and organelles cause cell death. Ongoing degenerative process in the mesocortical dopamine pathway explains a progressive worsening of symptoms and ever increasing deficit state in schizophrenia. [44]

### **Role of Conventional and atypical antipsychotics on various dimensions of schizophrenia**

Conventional antipsychotics act on D2 receptors of four dopamine pathways in the brain. [45]

- a. Positive symptoms especially delusions and hallucinations are reduced when mesolimbic D2 receptors are blocked.
- b. Negative and cognitive symptoms of psychosis get worsened when mesocortical D2 receptors are blocked,
- c. Blockade in the Nigrostriatal dopamine pathways may cause EPS and Tardive dyskinesia.
- d. D2 blockade in Tuberoinfundibular pathway cause hyper prolactinemia.

The search for drug that decreases the dopamine in mesolimbic area in order to treat positive symptoms and simultaneously increase dopamine in mesocortical area to treat negative and cognitive symptoms, while leaving dopamine tone unchanged in the Nigrostriatal and Tuberoinfundibular pathways to avoid side effects has resulted in the discovery of atypical antipsychotics.

Atypical antipsychotics also referred as serotonin and dopamine antagonists (SDAs). It is found that serotonin controls dopamine release from dopaminergic axonal terminals in the various dopamine pathways, but the degree of control varies across pathways. [46]

- Serotonin inhibits dopamine release, both at the level of dopamine cell bodies and at the level of dopaminergic axon terminals.
- Serotonin neurons from the brainstem raphe innervate the dopamine cell bodies in the substantia nigra and also project to the basal ganglia, where serotonin axon terminals are in close proximity to dopamine axonal terminals.
- In both areas serotonin interacts with postsynaptic serotonin 2A receptors on the dopamine neuron and this inhibits the dopamine release.
- Thus in the Nigrostriatal dopamine pathway, serotonin exerts powerful control over dopamine release at two levels. At level of serotonergic innervations of the Substantia Nigra, axon terminals arriving from the raphe synapse on the cell bodies and dendrites of dopaminergic cells. Then in both places serotonin interacts with dopamine via serotonin 2A receptors

Specific pharmacological properties of atypicals that distinguishes from conventional antipsychotics

1. Atypical have serotonin 2A and dopamine D2 antagonistic action where as conventional antipsychotics have only D2 antagonistic action
2. Atypical antipsychotics cause fewer EPS than conventional
3. Atypical improve both positive and negative symptoms where as conventional only positive symptoms.

### **Improvement of negative symptoms:**

The mesocortical dopamine pathway is hypothesized to be one of the contributing causes of negative symptoms of schizophrenia.

Serotonin 2A antagonism not only reverses dopamine 2 antagonism but also causes a net increase in dopamine activity in the

mesocortical dopamine pathway. Unlike Nigrostriatal pathway, in which dopamine 2 receptor predominate, there is preponderance of serotonin 2A receptors over dopamine 2 receptors in cerebral cortex.

The atypicals with SDA properties have effect in blocking densely populated cortical serotonin 2A receptors, thereby increasing DA release, than in blocking thinly populated cortical D2 receptors. This results in serotonin 2A antagonist binding and also dopamine release, but not much dopamine release in this part of the brain. This improves negative symptoms of schizophrenia.

- Clinical trials have shown that atypical antipsychotics improve negative symptoms better than either a placebo or conventional antipsychotics. [39]
- Positron Emission Tomography scan reveal that an antipsychotic dose of a conventional antipsychotic drug doesn't block serotonin 2A receptors in the cortex. Because these drugs lack such binding properties, but that an antipsychotic dose of atypical antipsychotic causes a nearly complete blockade of serotonin 2A receptors. Blockade of serotonin 2A receptors causes decrease in the dopamine, which explains in part why atypical antipsychotics improve negative symptoms better than conventional antipsychotics. [47]

Other neuro-chemical mechanisms are operative in the pathophysiology of negative symptoms but serotonin and dopamine make an important contribution as explained by the action in the mesolimbic pathway.

#### **Improvement of positive symptoms**

Serotonin 2A antagonism fortunately fails to reverse D2 antagonism in the mesolimbic system. Evidently, the

antagonism by serotonin of the effects of dopamine in this pathway is not robust enough to cause the reversal of D2 receptors by atypical antipsychotic or mitigate the action of atypical antipsychotics on positive symptoms of psychosis.

#### **Improvement of cognitive symptoms**

Cognitive impairment appears to be an integral characteristic of schizophrenia and may be evident in 60 % of patients. Measurable deficits are prominent in tasks involving attention, verbal fluency, memory, and executive function. The severity of cognitive symptoms correlates with long-term prognosis of schizophrenia and quality of life. [39,46,48]

The atypical antipsychotics improve cognition independent of their ability to improve positive symptoms. Improvement in global cognitive functioning with atypical antipsychotics may be secondary to less EPS and greater efficacy on negative symptoms. Studies have found there may be improvement in verbal fluency, serial learning, executive functioning memory and behavior. [49-52]

#### **Improvement of hostility aggression and poor impulse control**

Hostile and aggressive towards self in the form of suicidal attempt, self mutilation, poor impulse control, drug abuse, physical abuse, threatening behavior which may not correlate directly with positive symptoms.

Studies have found that this dimension of psychopathology that may not specific to the psychotic disorder may occur in other disorder but more common in psychotic illness than non-psychotic illness.

Suicidal behavior presents a particular problem in schizophrenics. Subjects having past history of suicidal behavior on atypical have shown lower rates than conventional. FDA has approved clozapine use in suicidal patients with schizophrenia based on InterSept study. [53]

## Improvement of depression and anxiety symptoms

Profound effects of atypical antipsychotics on the mood appear to be independent of its effect on positive symptoms.

- Hillert and colleagues first found evidence that risperidone reduced psychotic and affective symptoms.
- In a retrospective chart review found olanzapine either alone or in combination with antidepressants was effective in psychotic depression. [54]
- Clinical evidence has shown that some of the atypical antipsychotics have antidepressant effects in addition to antipsychotic properties. The efficacy is well documented, by its usefulness in mood disorder as mood stabilizing effect. Similarly its usefulness is found in the improvement of depression in schizophrenia. [49,55]
- A number of case reports and open trials have shown risperidone and olanzapine to be efficacious as monotherapy or adjunctive treatment for the treatment of depression without psychotic symptoms. [56,57]

## CONCLUSION

Disorganization, impairment and disability are the debilitating outcome of chronicity of schizophrenia pharmacological and non-pharmacological methods have failed to address these issues. Underpinning the neurobiological and genetic basis of causation of disorganization and negative symptoms prompts development of newer therapeutic interventions.

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