# INTRODUCTION

Schizophrenia (SCZ) is major mental illness that affects 1% of the world population and is associated with high suicide rates and disruption in social functioning **(Ross et al., 2006).** Symptoms develop either progressively or appear abruptly and vary from one patient to another. The disease evolves in cycles of remissions and relapses. Symptoms consist of separation from reality with delusion formation, hallucinations, emotional dis regulation and disorganized behaviour. Over time, a slow decline in mental function and social relationships occurs. This leads to a marked personality change, social isolation, occupational disability and cognitive impairment **(Carlborg et al., 2010).**

The presence of cognitive deficits is obvious in patients with psychotic disorders. These apply to most cognitive domains including working memory, verbal memory, executive function, attention, speed of information processing and visuo-spatial abilities **(Hauser et al., 2017),** it is suggested that cognitive impairments are present long before the onset of overt psychotic symptoms **(Mollon and Reichenberg, 2017).** However, despite their obvious significance for psychosis prediction as well as their importance for functional outcome, the neurobiological underpinnings behind the observed impairments remain largely unknown **(Ruiz de Azua et al., 2013).**

Brain-derived neurotrophic factor (BDNF) is a neurotrophin with purported roles in the development, regeneration, survival, and maintenance of neurons in the brain **(Nurjono et al., 2012).**

It is widely expressed in the brain that plays a key role in the regulation of neurogenesis and in the differentiation of neural pathways including dopaminergic pathways during neurodevelopment as well as in the modulation of synaptic plasticity and dendritic growth in the adult brain **(Nurjono et al., 2012)**.

Over the last years, the role of brain-derived neurotrophic factor (BDNF) in cognitive impairments in patients with psychosis has become a focus of interest **(Pezawas et al., 2004)**. Many evidence support the role of BDNF in modulating prefrontal cortex neuronal health and growth, the area which is responsible for executive functions and emotional regulations and this area became atrophic and defective with decreased BDNF levels as showed in mentally ill patients **(Yu and Chen, 2011)**.

BDNF is active during a critical developmental period and likely influences the neuroplasticity of schizophrenia **(Lu et al., 2014).** It has also been shown to modulate neurotransmitter synthesis, metabolism and release, regulate the long-term synaptic potentiation of neurons, and influence synaptic plasticity. BDNF has also been suggested to interact

with other neurotransmitter systems implicated in schizophrenia, such as dopamine, glutamate, serotonin and GABA **(Shoval and Weizman, 2005).**

It has been found that there is a change in BDNF level in several brain regions and in serum of patients with schizophrenia **(Ikeda et al., 2008).**

Better understanding of the pathophysiological mechanisms is therefore necessary to design better, targeted treatments, to enhance outcomes for patients with schizophrenia (**Steen et al., 2006).**

As antipsychotics are known to be the most effective treatment for schizophrenia, their potential role in neuroprotection might be related to BDNF **(Asevedo et al., 2013)** They are reported to influence BDNF levels to various degrees but the true influence of different antipsychotics on change in BDNF levels thus deserves further investigation **(Rizos et al., 2010)**.

In this study we aimed to investigate the effects of antipsychotics on serum BDNF levels in patients with drug-naïve first-episode schizophrenia. Finally, we examined whether the changes in serum BDNF levels are associated with the severity of clinical symptoms.

# RATIONALE

It is known that the worldwide prevalence of schizophrenia is approximately 1%. Schizophrenia may affect all aspects of patient's life; it affects not only him but also the family as a whole. It is a chronic disorder which may impact many aspects of patient's life including academic difficulties and social skills problems. It has been suggested that BDNF may play a role in the pathogenesis of schizophrenia and in cognitive impairment that may co – exist, this association has not been sufficiently studied among Egyptian patients. Also studies have explored the relationships between several antipsychotic agents and changes in BDNF levels but the true influence of different antipsychotics on change in BDNF levels deserves further investigation.

# HYPOTHESIS

The serum level of BDNF would be increased in patients with first episode schizophrenia after 6 weeks of treatment with atypical antipsychotics.

# AIM OF THE WORK

The aim of the study is:

- To determine the effects of atypical antipsychotics on serum BDNF levels in patients with schizophrenia
- To determine the effect of each atypical antipsychotic used on BDNF serum level
- To determine the relation between serum BDNF level and severity of symptoms.
- To determine the relationship between each of positive, negative, general symptoms and serum BDNF level.

## Chapter 1

# SCHIZOPHRENIA

**Schizophrenia** is a disorder of the executive function of both sensory and central nervous system (CNS). Although schizophrenia is characterized by a single disease, it is considered as a heterogeneous clinical syndrome affecting one's thoughts, feeling and acts **(Owen et al., 2016)**. Symptoms develop either progressively or appear abruptly and vary from one patient to another. The disease evolves in cycles of remissions and relapses. Symptoms consist of separation from reality with delusion formation, hallucinations, emotional dis regulation and disorganized behaviour. Over time, a slow decline in mental function and social relationships occurs. This leads to a marked personality change, social isolation, occupational disability, cognitive impairment and poor health; it is also a major cause of suicide **(Carlborg et al., 2010).**

## History

The word psychosis was introduced to the psychiatric literature in 1841 by Karl Friedrich Canstatt; Psychosis was first introduced in the mid-19th century for the separation of psychiatric disorders from neurological disorders within the neuroses **(Bürgy, 2008).**

The Latinized term dementia praecox was first used by German alienist Heinrich Schule in 1886 and then in 1891 by Arnold Pick in a case report of a psychotic disorder (hebephrenia). In 1893 Emil Kraepelin borrowed the term from Schule and Pick and in 1899 introduced a broad new distinction in the classification of mental disorders between dementia praecox and mood disorder (termed manic depression and including both unipolar and bipolar depression) **(Noll, 2011).** The Swiss psychiatrist, Eugen Bleuler, coined the term, "schizophrenia" in 1911. He was also the first to describe the symptoms as "positive" or "negative." Bleuler changed the name to schizophrenia as it was obvious that Krapelin's name was misleading as the illness was not a dementia and could sometimes occur late as well as early in life **(Ashok et al., 2012).**

In the early 20th century, the psychiatrist Kurt Schneider listed the forms of psychotic symptoms that he thought distinguished schizophrenia from other psychotic disorders. These are called first-rank symptoms or Schneider's first-rank symptoms. They include delusions of being controlled by an external force, the belief that thoughts are being inserted into or withdrawn from one's conscious mind, the belief that one's thoughts are being broadcast to other people, and hearing hallucinatory voices that comment on one's thoughts or actions or that have a conversation with other hallucinated voices **(Schneider, 1959).** Although they have significantly

contributed to the current diagnostic criteria, the specificity of first-rank symptoms has been questioned.

## Epidemiology

Schizophrenia occurs throughout the world. The prevalence of schizophrenia approaches 1 percent internationally. The incidence is about 1.5 per 10, 000 people. Slightly more men are diagnosed with schizophrenia than women (on the order of 1.4:1), and women tend to be diagnosed later in life than men. There is also some indication that the prognosis is worse in men **(McGrath et al., 2008).**

It is possible for schizophrenia to develop at any age, but it mostly happens to people within the ages of 16–30 (generally males aged 16–25 years and females 25–30 years); about 75 percent of people living with the illness developed it in these age-ranges (**Schizophrenia Society of Canada, 2011).** The earlier age of onset of schizophrenia in men than women may be due to the influence of the female sex hormone estrogen or due to socio-cultural influences **(Hochman and Lewine, 2004).**

The World Health Organization found the percentage of people affected and the number of new cases that develop each year is roughly similar around the world, with age-standardized prevalence per 100, 000 ranging from 343 in Africa to 544 in Japan and Oceania for men, and from 378 in Africa to 527 in Southeastern Europe for women **(Ayuso-Mateos, 2016).**

## Etiology and pathophysiology

It's not known what causes schizophrenia, but researchers believe that a combination of genetic and environmental factors play a role in the development of schizophrenia **(Owen et al., 2016).**

People with a family history of schizophrenia who have a transient psychosis have a 20–40% chance of being diagnosed one year later **(Drake and Lewis, 2005; Shetty & Bose, 2014).**

### *1) Genetic factors*

Although schizophrenia is very strongly heritable, not all cases are caused by heredity. Many people who appear to carry "schizophrenia genes" may not become schizophrenic **(Carlson, 2013)**.

Recent research suggests that genetic vulnerability to schizophrenia is multifactorial, caused by interactions of several genes **(Owen et al., 2005).**

**Twin studies** accumulating evidence shows that genetic and neurodevelopment factors are associated with greater susceptibility to schizophrenia. According to twin and adoption studies, up to 50% of identical (monozygotic) twins share a diagnosis of schizophrenia, compared with about 12% of non-identical (dizygotic) twins. The strength of genetic factors varies across families, but approximately 10% of a patient’s first-degree relatives (parents, siblings, and children) are also schizophrenic,

as are 50% of the children of two schizophrenic parents. Reports indicate suggestive linkage on chromosomes 1, 2, 3, 5, and 11 and on the X chromosome **(Mathews et al., 2013).**

**Family studies**: The paternal age is a factor in schizophrenia because of the increased likelihood of mutations in the chromosomes of cells that produce sperms. In contrast, women's oocytes divide twenty-three times before the time of birth and only once after that. The chance of a copying error in DNA replication during cell division increases with the number of cell divisions, and an increase in copying errors may cause an accumulation of mutations that are responsible for an increased incidence of schizophrenia **(Carlson, 2013).**

The largest most comprehensive genetic study of its kind, involving tests of several hundred single nucleotide polymorphisms (SNPs) in nearly 1, 900 individuals with schizophrenia or schizoaffective disorder and 2, 000 comparison subjects, reported in 2008 that there was no evidence of any significant association between the disorders and any of 14 previously identified candidate genes (RGS4, DISC1, DTNBP1, STX7, TAAR6, PPP3CC, NRG1, DRD2, HTR2A, DAOA, AKT1, CHRNA7, COMT, and ARVCF) **(Sanders et al., 2008).**

## *2) Biochemical factors*

The exact pathophysiology of schizophrenia remains poorly understood. The most commonly supported theories are the dopamine hypothesis and the glutamate hypothesis **(Elert, 2014).**

**Dopamine Hypothesis** Genetic evidence has suggested that there may be genes, or specific variants of genes, that code for mechanisms involved in dopamine function, which may be more prevalent in people experiencing psychosis or diagnosed with schizophrenia. Dopamine related genes linked to psychosis in this way include COMT, DRD4, and AKT1 **(Arguello et al., 2008).**

The dopamine systems in the mesolimbic pathway may contribute to the 'positive symptoms' of schizophrenia **(Carlson, 2013**) whereas problems with dopamine function in the mesocortical pathway may be responsible for the 'negative symptoms', such as avolition and alogia). Abnormal distribution of the $D_2$receptor between these areas and the rest of the brain may also be implicated in schizophrenia, specifically in the acute phase. A relative excess of these receptors within the limbic system means Broca's area, which can produce illogical language, has an abnormal connection to Wernicke's area, which comprehends language but does not create it **(McIntosh et al., 2008).**

The potency of an antipsychotic is proportional to its ability to antagonize dopamine D2/3 receptors. In early imaging studies based on positron emission tomography (PET), patients with schizophrenia showed increased dopamine activity in the striatum and the midbrain origin of neurons compared with the controls **(Yang & Tsai, 2017).**

**Glutamate hypothesis** beside the dopamine hypothesis, interest has also focused on the neurotransmitter glutamate and the reduced function of the NMDA glutamate receptor in the pathophysiology of schizophrenia. There is several mutations in genes related to glutamatergic neurotransmission, such as GRIN2A, GRIA1, SRR, and GRM3 **(Ripke et al., 2014).** Also it has largely been suggested by lower levels of glutamate receptors found in postmortem brains of people previously diagnosed with schizophrenia **(Konradi et al., 2003)** and the discovery that glutamate blocking drugs such as phencyclidine and ketamine can mimic the symptoms and cognitive problems associated with the condition **(Lahti et al., 2001)**

**Interneuron dysfunction** one that closely relates to the glutamate hypothesis, is one that evolves around dysfunction of interneurons in the brain **(Gonzalez-Burgos et al., 2015).** The largest meta-analysis on copy-number variations (CNVs), structural abnormalities in the form of genetic deletions or duplications for schizophenia, published in 2015, was the first genetic evidence for the broad involvement of GABAergic neurotransmission **(Pocklington et al., 2015).**

Their function is mainly through the inhibition of other cells. One type of interneuron, the fast-spiking, parvalbumin-positive interneuron, has been suggested to play a key role in schizophrenia pathophysiology (**Pittman-Polletta et al., 2015).**

Excitatory synapse density is lower selectively on parvalbumin interneurons in schizophrenia and predicts the activity-dependent down-regulation of parvalbumin and GAD67 together **(Chung et al., 2016).** Also it has been identified a decrease in GAD67 mRNA and protein in post-mortem brains from schizophrenia patients compared to controls **(Gonzalez-Burgos et al., 2010).**

### *3) Neuropathology and structural abnormalities*

Beside theories concerning the functional mechanism underlying the disease, structural findings have been identified as well using a wide range of imaging techniques **(Flashman & Green, 2004).**

The most consistent finding in post-mortem examinations of brain tissue is a lack of neurodegenerative lesions or gliosis. Abnormal neuronal organization and orientation (dysplasia) has been observed in the entorhinal cortex, hippocampus, and subcortical white matter, although results are not entirely consistent. A more consistent cytoarchitectural finding is reduced volume of purkinje cells and pyramidal cells in the hippocampus. This is consistent with

the observation of decreased presynaptic terminals in the hippocampus, and a reduction in dendritic spines in the prefrontal cortex. The reductions in prefrontal and increase in striatal spine densities seem to be independent of antipsychotic drug use **(Glausier et al., 2013).**

## Myelination abnormalities

Another hypothesis states that abnormalities in myelination are a core pathophysiology of schizophrenia **(Cassoli et al., 2015)**.

This theory originated from structural imaging studies, who found that white matter regions, in addition to grey matter regions, showed volumetric reductions in patients with schizophrenia, In addition, gene expression studies have shown abnormalities in myelination and oligodendrocytes in post-mortem brains of schizophrenia patients **(Stedehouder et al., 2017).**

It has been suggested that myelination abnormalities could originate from impaired maturation of oligodendrocyte precursor cells, as these have been found to be intact in schizophrenia brains **(Mauney et al., 2015).**

## Morphometry

Structural imaging studies have extensively reported differences in the size and structure of certain brain areas in schizophrenia. Abnormal findings in the prefrontal cortex,