

A Review of Brain-derived Neurotrophic Factor as a Candidate Biomarker in Schizophrenia

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Brain-derived neurotrophic factor (BDNF), a neurotrophin known to be responsible for development, regeneration, survival and maintenance of neurons has been implicated in the pathophysiology of schizophrenia. This review seeks to complement previous reviews on biological roles of BDNF and summarizes evidence on the involvement of BDNF in the pathophysiology of schizophrenia with an emphasis on clinical relevance. The expressions of BDNF were altered in patients with schizophrenia and were found to be correlated with psychotic symptomatology. Antipsychotics appeared to have differential effects on expression of BDNF but did not restore BDNF expression of patients with schizophrenia to normal levels. In addition, evidence suggests that BDNF is involved in the major neurotransmitter systems and is associated with disruptions in brain structure, neurodevelopmental process, cognitive function, metabolic and immune systems commonly associated with schizophrenia. Besides that, BDNF has been demonstrated to be tightly regulated with estrogen which has also been previously implicated in schizophrenia. Evidence gathered in this review confirms the relevance of BDNF in the pathophysiology of schizophrenia and the potential utility of BDNF as a suitable biomarker for diagnostic and prognostic purposes for disease outcome and other co-morbidities. However, further investigations are warranted to examine the specificity of BDNF in schizophrenia compared to other neurodegenerative disorders and other neuropsychiatric illness. Longitudinal prospective studies will also be of added advantage for evaluation of prognostic utility of BDNF in schizophrenia.

KEY WORDS: Schizophrenia; Brain-derived neurotrophic factor; Biomarkers.

INTRODUCTION

Schizophrenia is a severe mental illness that affects about 1% of the population.¹⁾ Schizophrenia is characterized by a myriad of signs and symptoms which include distortion of thinking and perception, cognitive impairments, motor abnormalities, avolition and apathy, difficulties in communication and restricted affective expression.²⁾ These symptoms are classified into three main domains: psychotic “positive symptoms”, deficits “negative symptoms” and cognitive dysfunction.³⁾ The etiology of the illness is complex and heterogeneous in nature, and remains unclear. In spite of our better understanding of several neurobiological alterations in brain structure, physiology and neurochemistry in patients in schizophrenia, there is currently no objective laboratory tool that can be used in the diagnosis, management and prognostic-

tion of schizophrenia.^{4,5)} Diagnosis of schizophrenia is made by reference to the set of clinical criteria in Diagnostic and Statistical Manual of Mental Disorders-IV and International Classification of Diseases-10 without an objective laboratory testing.⁴⁾

The lack of an objective tool has led to intensification of research into the search of suitable biomarker for diagnosis and management of schizophrenia. A substantial amount of evidence describes the role of brain-derived neurotrophic factor (BDNF) in the development, regeneration, survival and maintenance of neurons in the brain and its possible relevance in the pathophysiology of schizophrenia.⁶⁻⁸⁾ Much of the available reviews of the roles of BDNF in schizophrenia detailed the biological involvement of BDNF in schizophrenia. To complement to what has been previously reviewed, this manuscript aims to examine the role of BDNF in the pathophysiology of schizophrenia with an emphasis on clinical relevance. Cell biology of BDNF, recent association findings and association of BDNF with neurotransmitter systems, brain changes, stress, cognition, inflammation, metabolic disturbances and estrogen implicated in schizophrenia will

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be comprehensively examined.

CELL BIOLOGY OF BDNF

BDNF, a member of neurotrophins, was first purified by Barde *et al.*⁹⁾ in 1982 from pig's brain following neurotrophic growth factor. It is the most abundantly expressed neurotrophic factor found in the central nervous system (CNS).⁷⁾ Mature form of human BDNF is mapped to chromosome 11 and shares about 50% amino acid homology with other members of the neurotrophic factors such as nerve growth factor, neurotrophins-3 and neurotrophins 4/5. In humans, BDNF possess about 7 promoters and 8 axons and its gene expression relies on intracellular calcium (Ca^{2+}) expression which signals through Ca^{2+} dependent elements located in BDNF promoter III.¹⁰⁾ BDNF contains a signal peptide, a mature sequence and a distinctive 3-dimensional structure in homodimer for interactions with neurotrophin receptors.¹¹⁾

BDNF mRNA is widely distributed in the CNS and predominantly localized within neurons.^{11,12)} In mouse brain, BDNF mRNA becomes detectable during embryonic development, peaks by 10-14 days in the postnatal period and becomes widely distributed throughout the brain in adulthood with the highest concentration in the hippocampus.¹³⁾ Regulation of BDNF mRNA depends predominantly on neuronal activity via non *N*-methyl-D-aspartic acid (NMDA) receptor of glutamate system during upregulation and via *g*-aminobutyric acid (GABA) system for downregulation.¹²⁾ Neuronal expression of BDNF mRNA is highly dynamic and is affected by various physiological stimuli, neurotransmitters, hormones and pathological states.^{11,13)} In immature neurons, BDNF is involved in growth, differentiation, maturation and survival while mature neurons play an important role in synaptic plasticity, augmentation of neurotransmission and regulation of receptor sensitivity.¹⁴⁾

BDNF mRNA is translated in the endoplasmic reticulum into a precursor protein (pro-BDNF) which is folded in the trans Golgi, packaged into secretory vesicles and released primarily through the regulatory secretion pathway in response to stimuli or spontaneously through the constitutive pathway from the pre and post synaptic sites.^{7,15,16)} ProBDNF is then proteolytically cleaved into 14-kDa mature BDNF (mBDNF) by protease tissue plasminogen activator in response to neuronal activity.^{6,7,10)} Similar to mRNA, BDNF protein is widely distributed in the CNS in the neuronal cell bodies, axons and dendrites, particularly in the hippocampus where mossy fiber axons

are localized. BDNF proteins control high degree of neural plasticity important for learning and memory.^{11,17)} proBDNF and mBDNF are activated through binding with p75^{NTR} and TrkB receptor respectively. BDNF binding to p75^{NTR} initiates apoptotic like signaling cascade through various pathways while mBDNF selective binding to TrkB receptors initiate tyrosine phosphorylation in the cytoplasm which in turn activate cascade of events involved in cell survival, growth and differentiation.^{7,8,18)}

GENETIC POLYMORPHISM OF BDNF AND SCHIZOPHRENIA

Genetic associations between BDNF and schizophrenia have resulted in contradicting findings. Single nucleotide polymorphisms C270T, in 5' non coding region and Val66Met are the two common functional genetic polymorphisms of the BDNF gene. In some studies, significant association was observed between BDNF gene and schizophrenia. The frequency of individuals with this polymorphism and allele frequency C/T genotype and T allele are higher in patients with schizophrenia compared to healthy controls.^{19,20)} However, other studies failed to identify similar associations.²¹⁻²³⁾ No significant difference in allele or genotype frequencies were observed in a study of Han Chinese population which consisted of 353 patients with schizophrenia and 394 healthy volunteers²⁴⁾ but Val66Met minor allele frequency was found to be higher in the Armenian population.²⁵⁾ This difference is most probably due to the ethnic differences in allele frequencies.

Results from initial meta-analysis provided weak evidence of association between C270T polymorphism and schizophrenia²⁶⁾ while more recent meta-analysis showed that C-270T and Val66Met polymorphisms are not associated with susceptibility to schizophrenia in Asian and Caucasian populations.^{22,23,27)}

In spite of a lack of association between the two common polymorphisms with schizophrenia, Val66Met polymorphism has been investigated in relation to schizophrenia and correlated with features of the illness. This polymorphism affects dendritic trafficking, synaptic localization of BDNF and its secretion.^{7,15)} Val-BDNF was found to be localized to the cell body, dendrites and synapses while Met-BDNF is absent in the distal dendrites and synapses.^{10,16)} Val66Met BDNF mice demonstrated dendritic arborization defects in the hippocampus and significant reduction in hippocampal size.⁶⁾ Similarly, the right and left hippocampi were found to be reduced in in-

dividuals carrying the Met-BDNF polymorphism.²⁸⁾ In patients with schizophrenia, Met allele carriers showed significantly greater reductions in the frontal gray matter volume with a reciprocal volume increases in the lateral ventricles when compared to homozygous Val alleles carriers.⁶⁾ Within the parahippocampal gyrus, BDNF-Met allele related brain reduction was localized only on the right hemisphere of the brain.²⁹⁾ In addition, carriers of Met-BDNF polymorphism exhibit deficits in short term episodic memory and show abnormal hippocampal activation which commonly leads to cognitive dysfunctions.^{15,30,31)} Besides involvement in cognitive dysfunctions, a recent study revealed a significant association between genetic polymorphism of Val66Met with the presence of psychotic symptoms in males suffering from Alzheimer's Disease.³²⁾

Interestingly, females with homozygous Met/Met genotype had significantly lower mean serum BDNF levels compared to females carrying Val allele genotype.³³⁾ Different behavioural manifestations were also observed across individuals with different genotypes. Schizophrenic patients with BDNF Met/Val genotype were found to be more aggressive assessed using the modified overt aggression scale than patients with Val/Val genotype while Met/Met genotype patients were more aggressive than those with Val/Val genotype.³⁴⁾

Age of onset in male patients with schizophrenia was significantly associated with BDNF-Met polymorphism.²⁴⁾ Retrospective studies indicated that patients with schizophrenia who carries BDNF Met/Met genotype had a lower age of onset of the disorder compared to those with Val/Val or Val/Met genotypes.²⁵⁾

BDNF AND SCHIZOPHRENIA

Significant reduction of BDNF and TrkB receptors mRNA was observed in prefrontal cortex and hippocampus of patients with chronic schizophrenia.⁸⁾ In addition, similar reduction were also observed in the dentate gyrus and hippocampus.³⁵⁾ In cerebrospinal fluid (CSF), BDNF protein expression was reported to be reduced in acute and chronic psychotic patients.^{36,37)}

Outside the CNS, BDNF is expressed in the blood³⁸⁾ and its level in blood reflects BDNF levels in the CNS.³⁹⁾ In relation to schizophrenia, majority of studies showed a reduction of BDNF protein expression as detected through ELISA and western blotting in drug naïve patients with schizophrenia.⁴⁰⁻⁴²⁾ Similar reduction in BDNF was also observed in many studies examining chronic and

medicated patients with schizophrenia.^{33,43-46)} A meta-analysis that examined 16 studies which investigated the expression of BDNF in the blood indicated a moderate effect of reduction in blood of drug naïve and medicated patients with schizophrenia with increasing age.⁴⁷⁾ When investigated further through western blotting, serum pro-BDNF and mBDNF were observed to be increased while truncated form of BDNF was decreased in patients with schizophrenia.⁴⁸⁾ However, reintroduction of antipsychotics into drug free patients did not normalize the reduction of BDNF associated with illness.⁴²⁾

Severity of illness and outcome of treatments were commonly evaluated through improvements of symptoms using various rating scales. In a sample of 88 first-episode patients with schizophrenia and 90 healthy samples, serum BDNF levels were found to positively correlated with positive symptoms as measured using Positive and Negative Syndrome Scale (PANSS).⁴⁰⁾ Similar correlation was also observed in institutionalized Chinese patients with chronic schizophrenia.⁴⁵⁾ PANSS negative subscale scores, however, was found to be negatively correlated with serum BDNF level.^{44,46)} This observation was proposed to be due to the interaction of BDNF and dopamine.⁴⁰⁾

As chronic medicated patients with schizophrenia exhibit alteration of BDNF in the brain, CSF and blood, extensive studies have been performed to examine the effects of antipsychotics on BDNF levels. Animal studies showed that administration of antipsychotics altered brain BDNF levels. For example, haloperidol was shown to significantly reduce the level of BDNF as well as its TrkB receptor expression in the hippocampus while a switch to olanzapine was found to be associated with normalization of BDNF in sham animals.¹⁷⁾ In another study in rats, haloperidol and risperidone significantly decreased BDNF and TrkB receptor concentration in the frontal cortex, occipital cortex and hippocampus.⁴⁹⁾ Similarly, in patients with schizophrenia, a significant decrease in BDNF gene expression and immunoreactivity were detected in patients administered typical and atypical antipsychotics.⁴⁶⁾ The reduction of BDNF gene expression was believed to be a result of 5-HT receptor blockage as seen in patients on haloperidol and on high doses of risperidone.⁵⁰⁾ BDNF level was lowest in individuals taking risperidone, intermediate in those on clozapine and highest in those taking typical antipsychotics.⁵¹⁾ A recent study provided evidence that BDNF level was positively associated with clozapine daily dose in patients with schizophrenia.⁵²⁾ In addition, serum BDNF levels of patients of schizophrenia

were markedly lower in patients with schizophrenia with tardive dyskinesia (TD) which commonly results after a long exposure to antipsychotics when compared to those without TD.^{53,54)}

BDNF AND THE NEUROTRANSMITTERS

BDNF is a promising candidate as a biomarker for dysfunctions in the dopaminergic, glutamatergic and serotonergic neurotransmitter systems as BDNF levels are tightly coupled with dopaminergic and glutamatergic neurotransmitter systems.⁵⁵⁾ BDNF is synthesized by dopamine cells and is involved in the maintenance of the dopaminergic pathway. Destruction of midbrain dopamine cells was found to reduce BDNF mRNA expression which suggests that dopamine cells are essential for the synthesis of BDNF mRNA.⁸⁾ BDNF was also shown to improve the survival of dopamine neurons in culture and regulate Dopamine 1 (D1) and Dopamine 5 (D5) mRNA and protein expression in striatal astrocytes.⁸⁾ Another study provided evidence to suggest that BDNF is responsible for the appearance of Dopamine 3 (D3) receptor during the development and maintenance of D3 receptor expression in adults through control of specific dopamine genes.⁵⁶⁾ Besides that, BDNF was shown to be a modulator of dopaminergic function, and trigger behavioural sensitization by controlling D1 and D3 receptor expression and control dopamine tone in the limbic function.⁵⁷⁾ The activation of the signaling cascade that links BDNF and the dopaminergic pathway is believed to happen through mobilization of intracellular calcium which increases BDNF expression that accelerates morphological maturation and differentiation of striatal neurons as shown in adult rat brain.⁵⁸⁾

In the glutamatergic system, BDNF exerts neuroprotection and neuroactivation functions over excitatory and inhibitory neurons while being produced in excitatory neurons.⁸⁾ It increases presynaptic release of excitatory glutamatergic neurotransmitter and excitatory postsynaptic currents and reduces postsynaptic GABA receptors and inhibition.⁸⁾ BDNF promotes the development of GABA neurons and induces the expression of GABA-related protein such as glutamate decarboxylase 67 and glutamate transporter 1.⁶⁾ It regulates GABAergic signaling in cortex and other brain region to control plasticity in mouse visual cortex and cerebellar slices.⁶⁾

BDNF indirectly influences the development of serotonergic system by stimulating the expression of S100 beta in astrocytes and production of myelin basic protein in

oligodendrocytes.⁵⁹⁾ Evidence suggests that BDNF promotes the development and function of serotonergic neurons in survival and morphological differentiation of serotonin (5-HT) neurons *in vivo* and *in vitro*.^{6,15)} BDNF (+/-) heterozygous mice were observed to experience impairment in BDNF expression which in turn causes physiological disturbances in central 5-HT neurons leading to structural deterioration of these neurons in advanced age.⁶⁰⁾ In contrast, chronic administration of BDNF into rats was shown to increase the production of 5-HT neurons as indicated by the alteration in basal neurons firing.⁶¹⁾ In humans, enhanced serotonergic neurotransmission was found in humans with high BDNF serum concentrations.⁶²⁾

BDNF AND BRAIN CHANGES

Histological findings in schizophrenia revealed significant reductions in the size of neurons in the cortex⁶³⁾ and hippocampus^{64,65)} with fewer neurons in the dorsal thalamus.⁶⁶⁾ Reduction in synaptic and dendritic markers and maldistribution of white matter neurons were observed.^{3,66)} Since BDNF is known to play an important role in the growth and development of central and peripheral nervous system,^{67,68)} it is likely that BDNF is involved in the dysfunction of neuron development in patients with schizophrenia. Previously, BDNF was shown to regulate axonal and dendritic branching and BDNF signaling associated with adult neurogenesis, differentiation and survival of new neurons by increasing the number and length of axons and their branches.^{6,8,59,69)} In addition, BDNF exerts survival and growth promoting actions on CNS neurons. BDNF was demonstrated to promote survival of embryonic retina ganglion cells and mesencephalic dopaminergic neurons *in vitro*¹²⁾ and extensive neuronal outgrowth were observed following administration of BDNF in mice.¹¹⁾ Although, the association of histology of patients with serum BDNF has not been clearly shown, it is highly possible that the two are likely to be closely associated.

Along the same perspective, structural brain changes are observed in patients with schizophrenia early in the onset and at the chronic state of their illness as measured using magnetic resonance imaging. Various studies in first episode psychosis and schizophrenia demonstrated a significant reduction of brain volumes in patients compared to healthy controls.^{41,70,71)} A systematic review and meta analysis consisted of 52 cross sectional studies with a total of 1,424 patients revealed a significant reduction in hippo-

campal brain volume and enlargement of ventricles in first episode patients with schizophrenia.⁷²⁾ Similar observation was observed in chronic cases of schizophrenia. A longitudinal study of first episode patients revealed that antipsychotics treatment further reduced brain volume.⁷³⁾ When examined in relation to BDNF, reduction of brain volumes was found to be directly correlated with serum BDNF which is reduced in schizophrenia.⁴¹⁾

BDNF AND STRESS

Over the last decade, various neurobiological, neurocognitive, neuropathology and brain imaging studies collectively suggest that schizophrenia is a neurodevelopmental disorder that commonly starts early in life.^{3,74,75)} Retrospective studies found that individuals who developed schizophrenia often experienced pre and perinatal adverse events or harmful stressors.⁷⁵⁾ These individuals also experience impairments in their motor, cognitive and social development prior to onset of disease.^{75,76)}

Recent evidence suggests that stress is a common denominator between schizophrenia and BDNF. In rats, exposure to stress early in life induces decrease the expression of BDNF and to subsequent neuronal atrophy and degeneration in hippocampus and cortex which persist into adulthood.^{77,78)} In humans, childhood abuse was inversely correlated with serum BDNF in Val66Met carriers.⁷⁹⁾

An overlapping involvement of neurodevelopment implicated in schizophrenia makes BDNF an interesting potential candidate biomarker for schizophrenia. In patients with first episode psychosis, patients were found to have increased cortisol levels which was inversely correlated with serum BDNF. Logistic regression revealed that recent stressors and childhood trauma are predictive of lower BDNF gene expression which in turn increases interleukin-6 (IL-6), tumor necrosis factor (TNF)- α and cortisol level.⁷⁰⁾ Similarly in chronic patients with schizophrenia, negative correlation was observed between cortisol and BDNF levels in prefrontal cortex and CSF.³⁷⁾

BDNF AND COGNITION

Patients with schizophrenia experience cognitive impairments including learning, memory, attention, executive functioning, and cognitive processing speed.^{80,81)} Cognitive impairment is an enduring feature of schizophrenia which is often present at illness onset and persists regardless of a change in patients' psychopathology.⁸¹⁾

Cognitive impairments are major impediments to social rehabilitation and predict poor clinical outcome in patients with schizophrenia.⁸²⁾ Cognitive impairments observed in schizophrenia suggest that BDNF could be a potential biomarker candidate it is implicated in learning and memory.⁶⁾ BDNF plays a critical role in synaptic plasticity through NMDA receptor activation in the hippocampus.¹⁸⁾ BDNF increases the excitability of neurons by strengthening excitatory synapses and weakening inhibitory synapses affecting synaptic transmission.¹¹⁾ Hippocampal long term potentiation (LTP) which involves the strengthening of synapses as the result of binding of BDNF to TrkB receptor is responsible for learning and memory.⁶⁾ BDNF knock out mice and mice administered with function blocking anti-BDNF antibodies displayed impaired LTP and downstream learning and memory.^{8,11)} Impairment as the results of lack of BDNF was found to be restored by reintroduction of BDNF.

In exploration of association between cognition and BDNF, functional loss of one copy of BDNF gene was reported to result in cognitive impairments.⁸³⁾ In relation to schizophrenia, a study detected a significant positive correlation between the reduction in neurocognitive function and serum BDNF in 250 Chinese inpatients with schizophrenia.⁸⁰⁾ Cognitive enhancement using neuroplasticity based computerized cognitive training showed significant increase in serum BDNF compared to carefully matched controls.⁴³⁾ In another study, serum truncated BDNF abundance predicted a high cognitive deficits with 67.5% sensitivity and 97.5% specificity as obtained from receiver operating curve.⁸⁴⁾ This result suggests that deficiency in pro-BDNF processing may be involved in the mechanism underlying cognitive deficits observed in schizophrenia.

BDNF AND METABOLIC DISTURBANCES

Metabolic disturbances such as obesity, dyslipidemia, hyperglycemia and metabolic syndrome (MetS) are highly prevalent in individuals with BDNF deficiency, BDNF gene dysregulations as well as patients with schizophrenia.⁸⁵⁻⁸⁷⁾ Although the exact pathogenesis of these metabolic disturbances is unclear, they have been consistently shown to be risk factors for the development of cardiovascular diseases.⁸⁸⁻⁹⁰⁾ Studies have also reported increased mortality rate due to cardiovascular causes in patients with schizophrenia.⁹¹⁻⁹³⁾ While psychotic symptoms commonly improved, weight gain and metabolic perturbations persist following the administration of antipsychotics.

BDNF is highly relevant in this aspect of schizophrenia as recent evidence showed that BDNF was involved in metabolism and food regulation functions through appetite, weight and food consumption through its modulation in the hypothalamus.^{94,95)} Bulimia, obesity, hyperphagia, hyperinsulinemia and hyperglycemia were observed in mice heterozygous for BDNF or with BDNF deletion.^{60,96)} In human cases that alterations in BDNF gene led to childhood obesity and hyperphagia.⁸³⁾ Individuals with MetS exhibit a reduction in serum and plasma BDNF, with a greater reduction in the advanced stage of the illness. Besides that, BDNF level was found to be correlated with MetS criteria risk markers, body mass index, blood pressure and LDL-cholesterol.⁹⁷⁻⁹⁹⁾ This evidence supports the potential utility of BDNF as biomarker of schizophrenia as BDNF plays critical roles in regulation of the metabolic system which has been commonly known to be dysregulated in patients with schizophrenia.

BDNF AND INFLAMMATION

Since observation of increased risk of schizophrenia following prenatal infections, many studies have reported on the association between schizophrenia and immune related dysfunction. Although the typical manifestations characterized by gliosis and swelling were not observed in patients with schizophrenia, there is evidence to suggest that inflammatory related events are involved in schizophrenia. Inflammation related genes,¹⁰⁰⁾ leukocytes, white blood cell counts,¹⁰¹⁾ inflammatory cytokines,¹⁰²⁻¹⁰⁷⁾ pro-inflammatory monocytes,^{108,109)} immunoglobulins¹¹⁰⁾ and acute phase proteins¹¹¹⁾ were increased in the brains, serum, plasma and animal models of schizophrenia. Immune response type 1 was found to be suppressed and type 2 response was elevated in schizophrenia.¹¹⁰⁾ In addition, positron emission tomography scans revealed the presence of neuroinflammation as characterized by an increased microglia activity in the hippocampus of patients with schizophrenia.¹¹²⁾

BDNF is present outside the CNS and is circulated systematically. BDNF has been found to be synthesized, stored, and released not only by directly innervated cells but also by immune cells, vascular endothelial cells platelets, fibroblasts, myofibroblast, adipocytes and in the pancreatic beta-cell.^{98,99)} Analysis of BDNF production in lymphocyte revealed T-cells as a cellular source of BDNF in animal mouse model.¹¹³⁾ *In vitro*, activated human T-cells, B-cells and monocytes secrete bioactive BDNF.¹¹⁴⁾ BDNF is secreted by immune cells in response to neuro-

immune and inflammatory response as an act to protect the brain from any damage. An extensive review proposed that BDNF cross talk between the nervous and immune systems and play an important role in brain related disorders.¹¹⁵⁾ Based on these evidence, BDNF presents itself as a potentially useful biomarker to study the inflammatory features of schizophrenia which likely contributes to the persistent negative symptoms and cognitive features in schizophrenia. This hypothesis is further supported by the finding that BDNF serum level is inversely correlated with inflammatory marker IL-6 and TNF- α in psychosis.⁷⁰⁾

BDNF AND ESTROGEN

Literature reports suggested that estrogen is associated with schizophrenia. Significantly more males were found within patients with schizophrenia with male patients having earlier age of onset and more severe psychopathology compared to females.^{116,117)} In addition, low estrogen level was associated with worsening of symptoms and emerging evidence suggest that estrogen could be a neuroprotective and psychoprotective adjunctive therapy in the pharmacotherapy of schizophrenia.¹¹⁸⁾ Involvement of estrogen was suggested to be the result of changes in BDNF-TrkB signaling. Recently, full length TrkB receptor was reported to potentiate estrogen receptor alpha mediated transcription¹¹⁹⁾ as BDNF gene contains a sequence¹¹⁶⁾ the forebrain in regulation of the neurotransmitter systems.¹²⁰⁾ Estrogen regulated BDNF mRNA and protein expression.^{45,121)} Females were observed to exhibit a significantly higher expression of serum BDNF compared to their ethnicity and aged matched males counterparts.⁹⁷⁾ Likewise, in patients with schizophrenia, serum BDNF levels were differentially expressed with females having significantly higher BDNF expression.^{44,45,80)} Furthermore, treatment with estrogen increases BDNF mRNA in the hippocampus and protein expression in the septum of adult rat brain.^{121,122)} The potential roles of BDNF-TrkB signaling in regulation of estrogen implicated in schizophrenia further strengthen the potential utility of BDNF as biomarker.

CONCLUSION

Evidence gathered in this review suggests that BDNF is relevant in the pathophysiology of schizophrenia. The expression of BDNF is altered in schizophrenia, and correlates with psychotic symptomatology. In addition, the

body of evidence suggests that BDNF is involved in the major neurotransmitter systems and is associated with disruptions in brain structure, neurodevelopmental process, cognitive function, metabolic and immune systems commonly associated with schizophrenia. Besides that, BDNF has been demonstrated to be tightly regulated with estrogen which has also been implicated in schizophrenia.

Consistent BDNF mRNA and protein expression alterations in post mortem brain, plasma, serum and CSF samples in patients with schizophrenia suggest that it can be useful as a biomarker in schizophrenia. However, the specificity of BDNF as a biomarker of diagnosis for schizophrenia warrant further investigations as reduction in BDNF has also been observed in patients with neurodegenerative disorders and other neuropsychiatric illnesses. Perhaps, the truncated form of BDNF might be more accurate in identifying cases with schizophrenia while Val66Met BDNF polymorphism can be useful in predicting the age of onset of schizophrenia. In addition, due to the lack of prospective studies that examine the prognostic correlation between baseline BDNF and disease outcome, further investigations are needed to examine if BDNF can be a suitable marker of prognosis for schizophrenia.

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