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# BDNF as a pharmacogenetic target for antipsychotic treatment of schizophrenia

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# BDNF as a pharmacogenetic target for antipsychotic treatment of schizophrenia

## **Abstract**

Antipsychotic drugs remain the mainstay of pharmacotherapy for schizophrenia. As there are large individual variations in efficacy and side-effects of antipsychotic drugs, there is a strong demand for personalized medication to treat schizophrenia. Pharmacogenetic research into antipsychotic drugs has examined a number of genetic variants and only a few polymorphisms have been found which promise to be associated with the therapeutic efficacy and side-effects of antipsychotic drugs. Brain-derived neurotrophic factor (BDNF) is a neurotrophin that plays a major role in neurogenesis and neuroplasticity, and in the modulation of several neurotransmitter systems including the dopaminergic system involved in the pathophysiology of schizophrenia. This review focused on the association between the BDNF gene Val66Met polymorphism and antipsychotic drugs. The BDNF Val66Met polymorphism has been related to the pathophysiology of schizophrenia, psychotic symptomatology, cognition, efficacy and side-effects of antipsychotic drugs. The BDNF Val66Met variants could be a promising target for antipsychotic medication options or developing next generation antipsychotic drugs. However, some studies showed inconsistent results due to sample size, ethnic differences and different antipsychotic drugs. Further studies will be required in this area to confirm the effect of the BDNF Val66Met polymorphism in the pathophysiology of schizophrenia and patients' response to antipsychotic drugs, especially in a larger sample size and in different ethnic populations.

## **Disciplines**

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## **BDNF as a pharmacogenetic target for antipsychotic treatment of schizophrenia**

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## **Abstract**

Antipsychotic drugs remain the mainstay of pharmacotherapy for schizophrenia. As there are large individual variations in efficacy and side-effects of antipsychotic drugs, there is a strong demand for personalized medication to treat schizophrenia. Pharmacogenetic research into antipsychotic drugs has examined a number of genetic variants and only a few polymorphisms have been found which promise to be associated with the therapeutic efficacy and side-effects of antipsychotic drugs. Brain-derived neurotrophic factor (BDNF) is a neurotrophin that plays a major role in neurogenesis and neuroplasticity, and in the modulation of several neurotransmitter systems including the dopaminergic system involved in the pathophysiology of schizophrenia. This review focused on the association between the *BDNF* gene Val66Met polymorphism and antipsychotic drugs. The *BDNF* Val66Met polymorphism has been related to the pathophysiology of schizophrenia, psychotic symptomatology, cognition, efficacy and side-effects of antipsychotic drugs. The *BDNF* Val66Met variants could be a promising target for antipsychotic medication options or developing next generation antipsychotic drugs. However, some studies showed inconsistent results due to sample size, ethnic differences and different antipsychotic drugs. Further studies will be required in this area to confirm the effect of the *BDNF* Val66Met polymorphism in the pathophysiology of schizophrenia and patients' response to antipsychotic drugs, especially in a larger sample size and in different ethnic populations.

**Key words:** antipsychotic drugs; brain-derived neurotrophic factor; genetic variants; polymorphisms; schizophrenia

## 1. Introduction

Schizophrenia exhibits complex and serious symptoms which vary extensively between individuals. Antipsychotic drugs have remained the mainstay of pharmacotherapy for schizophrenia over the past 60 years. Antipsychotic drugs are generally divided into typical and atypical agents. Typical antipsychotics such as haloperidol mainly bind to dopamine D2 receptors, which often cause extrapyramidal symptoms (EPS), and even irreversible tardive dyskinesia (TD) [1, 46]. Compared to typical antipsychotics, besides blockage of D2 receptors, atypical antipsychotics including olanzapine and clozapine have more diverse receptor binding profiles such as the 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors, which are less frequently accompanied by EPS and TD, but are often associated with side-effects such as obesity and other metabolic disorders [46]. Importantly, there are larger individual variations in the therapeutic efficacy and in the side-effects of antipsychotic drugs, while only about 50% of patients treated with antipsychotic drugs present improvement in clinical symptoms [23]. Moreover, a study showed an average 74% (range from 64%-82% for different antipsychotic drugs) of schizophrenia patients discontinued their assigned medication within 18 months, mainly due to their lack of efficacy and intolerable side-effects [21].

Family and twin studies suggest that individual differences in schizophrenia patients in symptoms, therapeutic response and side-effects of antipsychotic drugs are significantly related to genetic differences. Therefore, the pharmacogenetics of antipsychotic drugs may provide important evidence that genetic variation influences patients' response and intolerance to antipsychotic drugs. However, although the pharmacogenetics of antipsychotic drugs in dopamine and serotonin receptors such as D<sub>2</sub>, D<sub>3</sub>, 5-HT<sub>2A</sub>, and 5-HT<sub>2C</sub> receptors, as well as their metabolic pathways including COMT and CYP2D6, showed some promising

findings [49], current results are still long away from explaining the individual variations in therapeutic responses, and side-effects of antipsychotic drugs.

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family of growth factors [40]. BDNF is the most widely distributed neurotrophin in the central nervous system, especially in the prefrontal cortex (PFC), hippocampus and hypothalamus, and plays critical roles in brain neurodevelopment, and maintenance of functional neurons and synaptic plasticity [40]. Decreased serum BDNF levels have been found in both first-episode and chronic schizophrenia patients [37, 39]. Serum BDNF levels have been shown to be positively correlated with positive symptoms and negatively correlated with negative symptoms of schizophrenia [37, 39]. BDNF protein expression has been found to be reduced not only in blood serum but also cerebrospinal fluid (CSF) in both acute and chronic schizophrenia patients [37, 50]. Reduced expression of BDNF and its highly affiliated tropomyosin receptor kinase B (TrkB) have been found in the PFC and hippocampus of schizophrenia patients [30]. Thus BDNF should be a valuable candidate gene for pharmacogenetic analysis of antipsychotic drugs.

The *BDNF* gene is located on chromosome 11p13. Several investigations into the role of *BDNF* gene polymorphisms have been conducted to establish both the efficacy and side-effects of antipsychotics, and have had mixed outcomes [18, 25, 48]. The *BDNF* gene Val66Met (rs6265) polymorphism, which results in methionine (Met) substitution for valine (Val) at codon 66 in the 5' pro-region of the gene, is a common functional single nucleotide polymorphism (SNP) of *BDNF*. This review is mainly focused on the *BDNF* gene Val66Met polymorphism in antipsychotic efficacy and side-effects. It aims to provide evidence that the

*BDNF* gene could be worth prioritising for pharmacogenetics' research into antipsychotic drugs and its potential relevance to their treatment response and side-effects.

## **2. *BDNF* Val66Met polymorphism and clinical and pathophysiological characteristics of schizophrenia**

In spite of some inconsistent findings about the association between *BDNF* Val66Met polymorphism and schizophrenia [13, 44], the *BDNF* Val66Met polymorphism has been found to be significantly associated with several clinical and pathophysiological characteristics of the illness, such as age of onset, symptoms and brain pathology [19, 28]. While the frequency of the Met/Met genotype in schizophrenia was significantly higher in those patients presenting mainly positive symptoms compared to those with negative symptoms [34], a recent study showed a significant association between the Val66Met polymorphism and negative symptoms severity in first episode schizophrenia spectrum disorders [24]. Schizophrenia patients carrying the *BDNF* Met/Met genotype have more delusional symptoms than 66Val allele carriers [15]. Schizophrenia patients who carry the *BDNF* Val/Met genotype had higher scores on a hallucinatory behaviour item than those with other genotypes [34]. An association between the *BDNF* Val66Met polymorphism and obsessive-compulsive symptoms has also been found in Egyptian schizophrenia patients [16]. A Met carrier of the *BDNF* Val66Met genotype is associated with lower serum BDNF levels [43]. While the *BDNF* Val66Met polymorphism is not associated with hippocampal volume change over time in schizophrenia patients, there are smaller hippocampal volumes in patients homozygous for the Val allele compared to healthy Val homozygotes [20].

It should be pointed out that some associations between the *BDNF* Val66Met and clinical and pathophysiological characteristics of schizophrenia are not always consistent, and some

results are difficult to explain. For example, schizophrenia patients carrying the *BDNF* Met/Met genotype had a lower age of onset compared to those with Val/Val or Val/Met genotypes in an Armenian population [44]. However, another study found that schizophrenia patients with the Val/Met genotype had an earlier onset age than those with other genotypes in a Polish population [34]. These inconsistent findings between the *BDNF* Val66Met polymorphism and age at onset of schizophrenia may be attributed to ethnic difference, which warrants further investigation in a larger sample or different ethnic populations.

### **3. *BDNF* Val66Met polymorphism and cognitive deficits**

Cognitive deficits are the core and enduring feature of schizophrenia, and include impairment of learning, memory, attention and cognitive processing speed. Neuroimaging studies have documented that the hippocampus plays a crucial role in these important cognitive functions [3]. Serum BDNF levels were identified to be associated with reductions in hippocampal volume in first-episode and drug-naive schizophrenic patients [31]. Generally, it is thought that typical antipsychotics are related to cognitive deterioration and atypical antipsychotics are associated with statistically significant but small improvements in cognition in schizophrenia patient treatments. However, high dose of atypical antipsychotics (e.g. 5-6 mg risperidone equivalents per day) may be associated with poorer cognitive performance in schizophrenia patients [10]. Importantly, BDNF serum levels are decreased and positively correlated with cognitive deficits in schizophrenia patients [51]. A recent study has found that olanzapine improves cognition especially for attention and immediate memory, which parallels increased plasma BDNF levels in acute onset of schizophrenia patients [54]. However, chronic treatment of olanzapine could cause metabolic syndrome in some (~44%) schizophrenia patients correlated significantly with cognitive impairment, in which these patients also had a significant lower BDNF levels than those without metabolic syndrome,



suggesting an interactive role of BDNF in the metabolic side-effects of olanzapine on cognitive function [45].

It is interesting that the *BDNF* Met variant is related to poor visuospatial and attention impairment in schizophrenia patients [41]. *BDNF* Val/Val genotype carriers showed better working memory than Val/Met and Met/Met genotype carriers in schizophrenia patients [32]. These findings supported that the *BDNF* Val66Met polymorphism might be significantly involved in the cognitive deficits of schizophrenia. On the other hand, carriers of the Met *BDNF* polymorphism exhibit cognitive deficits in episodic memory and abnormal hippocampal activation which commonly leads to cognitive dysfunction in both healthy populations and schizophrenia patients [9, 36]. However, another study reported that the 66Met allele did not affect episodic memory in schizophrenia patients [7]. Although there are still some controversies, the *BDNF* Val66Met may be a new target to consider in developing new generation antipsychotic drugs for improving cognitive deficits for schizophrenia treatment.

#### **4. BDNF Val66Met polymorphism and efficacy of antipsychotic drugs**

BDNF modulates the major neurotransmitter systems including the dopaminergic, glutamatergic, and serotonergic systems [14, 28, 49]. It is well known that dopamine D2 receptor antagonism is a unifying property of all antipsychotic drugs. Olanzapine treatment improves the reduced BDNF serum levels in first-episode or acute onset schizophrenia patients [12, 54]. Therefore, BDNF is significantly involved in the effects of antipsychotic drug treatment.

Importantly, the *BDNF* Val/Val genotype and Val allele were found to be over-represented in the responder group compared to the non-responder group with various antipsychotic treatments including clozapine, olanzapine and others (Table 1) [42]. The *BDNF* Val/Val genotype was observed more frequently in treatment responders to olanzapine compared to other antipsychotic drugs including clozapine treatment, and this genotype was associated with an improvement in clinical symptoms (Table 1) [29]. Moreover, better treatment response to olanzapine was also associated with higher plasma *BDNF* levels in the Val/Val homozygous genotype in schizophrenia patients [27]. The potential mechanism of increased response to antipsychotic drugs of the *BDNF* Val/Val genotype and Val allele group is not clear. However, a study has shown that the *BDNF* Met allele may affect intracellular distribution, packaging, and release of *BDNF* protein [9]. Also, the *BDNF* Val/Val genotype is associated with an increased synaptic plasticity and increased activity-dependent *BDNF* release [9]. Therefore, we hypothesise that the *BDNF* Val/Val genotype or Val allele in schizophrenia patients may show a better response to antipsychotic drugs, particularly olanzapine, by increased *BDNF* release and synaptic plasticity.

Although studies support that the *BDNF* Val66Met variants may be significantly involved in the therapeutic response to antipsychotic drugs in schizophrenia treatment, there are a series of inconsistent findings (Table 1). For example, one study showed that there were no significant differences in therapeutic response to clozapine treatment among the three Val66Met-genotype subgroups in schizophrenia patients [17]. There is a greater incidence of the *BDNF* Met/Met genotype in patients with treatment resistant response to typical antipsychotics in the Caucasian population [47], however another study found a lack of association between the *BDNF* Val66Met polymorphism and patients' response to typical antipsychotics in the Finnish population [2]. Therefore, the effects of the *BDNF* Val66Met

polymorphism in antipsychotic drugs need to be further confirmed in schizophrenia treatment especially in different ethnic populations, a larger sample size and different antipsychotic drugs.

### **5. BDNF Val66Met polymorphism and metabolic disorders**

Metabolic disorders such as weight gain, insulin resistance and diabetes are common and serious side-effects of antipsychotics, especially for atypical antipsychotic drugs [6, 8]. A recent meta-analysis in 25 studies with 154,718 schizophrenia and 4,343,407 control subjects showed antipsychotic treatment led to 2.5 times higher risk of type 2 diabetes (T2D) [33]. Several lines of evidence support that *BDNF* Met66 polymorphism is an essential contributor to the regulation of food intake, body weight gain and other metabolic disorders. For example, a meta-analysis showed that the *BDNF* Met66 allele increases the risk for eating disorders by 36% in bulimia nervosa or binge eating disorders [26]. The *BDNF* Val66Met is associated with not only obesity but also T2D [35]. A recent study showed that the *BDNF* Val66Met is positively associated with high BMI in schizophrenia patients, while bipolar disorder subjects with Met66Met genotype showed increase in the triglycerides/high-density (HDL) cholesterol ratio, a key marker for metabolic syndrome related to insulin resistance [4].

Importantly, *BDNF* Met variants were found to be significantly associated with obesity, weight gain and lipid metabolic disorders for schizophrenia patients treated with antipsychotic drugs (Table 1) [4, 53], while this weight gain side-effects of antipsychotic drugs in schizophrenia patients was also observed for the two-marker haplotype of *BDNF* across Val66Met and rs1519480 [42]. The *BDNF* Met allele was associated with increased insulin resistance in the schizophrenia population but not in the bipolar population treated

with atypical antipsychotics, which suggests that glucose regulation is more dependent on genetic factors like the *BDNF* gene in schizophrenia patients (Table 1) [5]. These results provide supporting evidence that the *BDNF* Val66Met plays a significant role in metabolic disorders for schizophrenia patients treated with antipsychotic drugs. However, how the *BDNF* Val66Met affect BDNF activity and leads to metabolic disorders is not well known. Whether the *BDNF* 66Met allele has a significant impact on intracellular trafficking and activity-dependent secretion of BDNF in brain region-specific manner need further investigation, especially in hypothalamic nuclei associated with eating behaviour, food consumption, and control of body weight [9]. Moreover, a study showed that *BDNF* Met66Met genotype has a strong relationship with BMI gain in male but not female schizophrenia patients [53]. Therefore, the effects of *BDNF* Val66Met on metabolic disorders induced by antipsychotics are needed for further investigations, especially longitudinal studies with larger sample sizes in schizophrenia patients.

In addition, as discussion as above, the *BDNF* Val66Met might be involved in the aetiology and pathophysiology of both schizophrenia and metabolic disorder [13, 26, 35, 44]. Schizophrenia patients are also observed to have a higher morbidity of metabolic disorders than the general population although this might be partly due to antipsychotic treatment [11]. Further investigation is necessary to reveal whether the co-morbidity link between the two diseases are influenced by shared *BDNF* genetic variants, especially *BDNF* Val66Met, via the pleiotropic effects (i.e., the same DNA sequence causes the psychopathology inherent in schizophrenia and altered glucose metabolism).

## **6. BDNF Val66Met polymorphism and EPS**

EPS including acute dystonia, akathisia and TD are normal and serious side-effects caused by antipsychotic drugs. Acute EPS are one of the main causes of noncompliance with antipsychotic treatment, while TD has the most serious impact on quality of life for schizophrenia patients. TD is a motor system disorder and potentially irreversible side-effect that is characterised by repetitive and involuntary movements experienced by about 20-50% of patients treated with long-term antipsychotic drugs, especially for typical antipsychotics [38]. Serum BDNF levels are lower in schizophrenia patients with TD compared to those without TD [52]. BDNF is found to increase the functions of the nigrostriatal dopaminergic system, a brain region implicated in the pathogenesis of TD and a major target area for antipsychotics. Therefore, BDNF may be involved in TD caused by treatment of schizophrenia with antipsychotics, especially for typical antipsychotics.

A meta-analysis and other studies showed that Caucasian *BDNF* Met allele carriers had significantly higher TD occurrence than Asian patients treated with antipsychotics [18,22, 25]. In addition, a Chinese population study indicated that the *BDNF* gene Val66Met polymorphism did not contribute to genetic susceptibility to TD or its severity [52]. However, treatment with Ginkgo biloba improved TD significantly more in the *BDNF* genotype of Val/Val than in the Val/Met or Met/Met genotypes in schizophrenia patients [52]. Another ethnic Chinese study showed that the *BDNF* val66met polymorphism did not play a significant role in the susceptibility to TD of chronic antipsychotic treatment, but exerted its effect on the clinically phenotypic variability in persistent TD patients [22]. These results support that the *BDNF* Val66Met polymorphism might be involved in TD after antipsychotic treatments in schizophrenia patients especially for the Caucasian populations. However, it is important to point out that a smaller number of Caucasian patients (19.5% compared to 80.5% Asians) has been used in this meta-analysis to reveal an association between *BDNF*

Val66Met polymorphism and TD [25]. Further studies in an extend sample size are needed for confirming the association between *BDNF* Val66Met variants and antipsychotic-induced TD in schizophrenia patients, particularly in Caucasian population.

## **Conclusion**

Schizophrenia patients have large individual differences in clinical symptoms and response to antipsychotic drugs. Therefore, personalized medications are required in schizophrenia treatment. This review has provided evidence that the *BDNF* Val66Met polymorphism is significantly associated with the pathophysiology of schizophrenia, psychotic symptomatology, cognition, efficacy and side-effects of antipsychotic drugs. The *BDNF* Val66Met variants should be considered as a pharmacogenetic target for antipsychotic drugs or developing the next generation of antipsychotic drugs. However, there are some inconsistent findings in the association between the *BDNF* Val66Met polymorphism, clinical symptoms or response to antipsychotic drugs in schizophrenia treatment which needs further confirmation, especially in a larger sample size and in different ethnic populations. Furthermore, the associations between other *BDNF* genetic variants and response to antipsychotic drugs in schizophrenia patient are also necessary to be investigated.

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**Table 1**

The association between *BDNF* Val/Met polymorphism and efficacy and side-effects of antipsychotic drugs in schizophrenia treatment.

Studies	Sample size	Study design Investigating	Main findings
Zai et al. [42]	257	The role of <i>BDNF</i> Val/Met variants in antipsychotic response	Val/Val genotype and Val allele more presented in response patients
Perkovic et al. [29]	590	The association between <i>BDNF</i> Val/Met variants and therapeutic response to olanzapine	Val/Val genotype more frequently in treatment responders to olanzapine
Hong et al. [17]	93	The association of <i>BDNF</i> Val/Met variants with clozapine response	No significant association
Zhang et al. [47]	279	The association of <i>BDNF</i> Val/Met variants with antipsychotic treatment resistance	Met/Met genotype associated with antipsychotic treatment resistance
Anttila et al. [2]	94	The association of <i>BDNF</i> Val/Met variants with patients' response to typical antipsychotics	No significant association
Bonaccorso et al. [4]	166	The effects of <i>BDNF</i> Val/Met variants in BMI and insulin resistance	Met66 carriers treated with risperidone had the greatest increase in BMI and abnormal lipid levels
Zhang et al. [53]	196	The role of <i>BDNF</i> Val/Met variants in antipsychotic-induced BMI gain	Met66Met genotype associated with BMI gain in male but not female patients
Burghardt et al. [5]	252	The influence of <i>BDNF</i> Val/Met variants in insulin resistance	66Met allele associated with insulin resistance
Miura et al. [25]	1740	<i>BDNF</i> Val66Met polymorphism and antipsychotic-induced TD. A Meta-analysis	Although no significant association, it affects TD severity in Caucasians
Kang et al. [18]	209	The association between <i>BDNF</i> Val/Met variants and TD	No significant association in Korean patients
Liou et al. [22]	216	The role of <i>BDNF</i> Val/Met variants in antipsychotic-induced TD	Val66Met genotype had higher TD occurrence than Met/Met or Val/Val genotype patients in Chinese